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(54) Title: INHIBITORS OF HISTONE DEACETYLASE

(57) Abstract: The invention relates to the inhibition of histone deacetylase. The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions.



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INHIBITORS OF HISTONE DEACETYLASE

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Application 10/358,556.

BACKGROUND OF THE INVENTION

Field of the Invention

[0002] This invention relates to the inhibition of histone deacetylase. More particularly, the invention relates to compounds and methods for inhibiting histone deacetylase enzymatic activity.

Summary of the Related Art

[0003] In eukaryotic cells, nuclear DNA associates with histones to form a compact complex called chromatin. The histones constitute a family of basic proteins which are generally highly conserved across eukaryotic species. The core histones, termed H2A, H2B, H3, and H4, associate to form a protein core. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. Approximately 146 base pairs of DNA wrap around a histone core to make up a nucleosome particle, the repeating structural motif of chromatin.

[0004] Csordas, *Biochem. J.*, 286: 23-38 (1990) teaches that histones are subject to posttranslational acetylation of the α -amino groups of N-terminal lysine residues, a reaction that is catalyzed by histone acetyl transferase (HAT1). Acetylation neutralizes the positive charge of the lysine side chain, and is thought to impact chromatin structure. Indeed, Taunton et al., *Science*, 272: 408-411 (1996), teaches that access of transcription factors to chromatin templates is enhanced by histone hyperacetylation. Taunton et al. further teaches that an enrichment in underacetylated histone H4 has been found in transcriptionally silent regions of the genome.

[0005] Histone acetylation is a reversible modification, with deacetylation being catalyzed by a family of enzymes termed histone deacetylases (HDACs). Grozinger et al., *Proc. Natl. Acad. Sci. USA*, 96: 4868-4873 (1999), teaches that HDACs is divided into two classes, the first represented by yeast Rpd3-like proteins, and the second

represented by yeast Hda1-like proteins. Grozinger et al. also teaches that the human HDAC1, HDAC2, and HDAC3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC4, HDAC5, and HDAC6, which are members of the second class of HDACs. Kao et al., *Genes & Dev.*, 14: 55-66 (2000), discloses HDAC7, a new member of the second class of HDACs. Van den Wyngaert, *FEBS*, 478: 77-83 (2000) discloses HDAC8, a new member of the first class of HDACs.

[0006] Richon et al., *Proc. Natl. Acad. Sci. USA*, 95: 3003-3007 (1998), discloses that HDAC activity is inhibited by trichostatin A (TSA), a natural product isolated from *Streptomyces hygroscopicus*, and by a synthetic compound, suberoylanilide hydroxamic acid (SAHA). Yoshida and Beppu, *Exper. Cell Res.*, 177: 122-131 (1988), teaches that TSA causes arrest of rat fibroblasts at the G₁ and G₂ phases of the cell cycle, implicating HDAC in cell cycle regulation. Indeed, Finnin et al., *Nature*, 401: 188-193 (1999), teaches that TSA and SAHA inhibit cell growth, induce terminal differentiation, and prevent the formation of tumors in mice. Suzuki et al., U.S. Pat. No. 6,174,905, EP 0847992, JP 258863/96, and Japanese Application No. 10138957, disclose benzamide derivatives that induce cell differentiation and inhibit HDAC. Delorme et al., WO 01/38322 and PCT IB01/00683, disclose additional compounds that serve as HDAC inhibitors.

[0007] The molecular cloning of gene sequences encoding proteins with HDAC activity has established the existence of a set of discrete HDAC enzyme isoforms. Grozinger et al., *Proc. Natl. Acad. Sci. USA*, 96:4868-4873 (1999), teaches that HDACs may be divided into two classes, the first represented by yeast Rpd3-like proteins, and the second represented by yeast Hda1-like proteins. Grozinger et al. also teaches that the human HDAC-1, HDAC-2, and HDAC-3 proteins are members of the first class of HDACs, and discloses new proteins, named HDAC-4, HDAC-5, and HDAC-6, which are members of the second class of HDACs. Kao et al., *Gene & Development* 14:55-66 (2000), discloses an additional member of this second class, called HDAC-7. More recently, Hu, E. et al. *J. Bio. Chem.* 275:15254-13264 (2000) discloses the newest member of the first class of histone deacetylases, HDAC-8. It has been unclear what roles these individual HDAC enzymes play.

[0008] These findings suggest that inhibition of HDAC activity represents a novel approach for intervening in cell cycle regulation and that HDAC inhibitors have great therapeutic potential in the

treatment of cell proliferative diseases or conditions. To date, few inhibitors of histone deacetylase are known in the art. There is thus a need to identify additional HDAC inhibitors and to identify the structural features required for potent HDAC inhibitory activity.

BRIEF SUMMARY OF THE INVENTION

[0009] The invention provides compounds and methods for treating cell proliferative diseases. The invention provides new inhibitors of histone deacetylase enzymatic activity.

[0010] In a first aspect, the invention provides compounds that are useful as inhibitors of histone deacetylase.

[0011] In a second aspect, the invention provides a composition comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent.

[0012] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase of the invention.

[0013] The foregoing merely summarizes certain aspects of the invention and is not intended to be limiting in nature. These aspects and other aspects and embodiments are described more fully below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 is a graph showing the antitumor activity of compound 106 in an HCT 116 human colorectal tumor model.

[0015] Figures 2-11 show additional data for other compounds used in the *in vivo* experiment described in Assay Example 2.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0016] The invention provides compounds and methods for inhibiting histone deacetylase enzymatic activity. The invention also provides compositions and methods for treating cell proliferative diseases and conditions. The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure will prevail.

[0017] For purposes of the present invention, the following definitions will be used (unless expressly stated otherwise):

[0018] As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the α -amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context, the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Preferred histone deacetylases include class I and class II enzymes. Preferably the histone deacetylase is a human HDAC, including, but not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8. In some other preferred embodiments, the histone deacetylase is derived from a protozoal or fungal source.

[0019] The terms "histone deacetylase inhibitor" and "inhibitor of histone deacetylase" are used to identify a compound having a structure as defined herein, which is capable of interacting with a histone deacetylase and inhibiting its enzymatic activity.

"Inhibiting histone deacetylase enzymatic activity" means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. In some preferred embodiments, such reduction of histone deacetylase activity is at least about 50%, more preferably at least about 75%, and still more preferably at least about 90%. In other preferred embodiments, histone deacetylase activity is reduced by at least 95% and more preferably by at least 99%.

[0020] Preferably, such inhibition is specific, i.e., the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce another, unrelated biological effect. Preferably, the concentration of the inhibitor required for histone deacetylase inhibitory activity is at least 2-fold lower, more preferably at least 5-fold lower, even more preferably at least 10-fold lower, and most preferably at least 20-fold lower than the concentration required to produce an unrelated biological effect.

[0021] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (e.g., alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural

circumstances clear to those skilled in the art. For example, while an "alkyl" moiety generally refers to a monovalent radical (e.g. $\text{CH}_3\text{-CH}_2\text{-}$), in certain circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g., $\text{-CH}_2\text{-CH}_2\text{-}$), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene.) All atoms are understood to have their normal number of valences for bond formation (i.e., 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). On occasion a moiety may be defined, for example, as $(\text{A})_a\text{-B-}$, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-. Also, a number of moieties disclosed herein exist in multiple tautomeric forms, all of which are intended to be encompassed by any given tautomeric structure.

[0022] The term "hydrocarbyl" refers to a straight, branched, or cyclic alkyl, alkenyl, or alkynyl, each as defined herein. A " C_0 " hydrocarbyl is used to refer to a covalent bond. Thus, " $\text{C}_0\text{-C}_3\text{-hydrocarbyl}$ " includes a covalent bond, methyl, ethyl, propyl, and cyclopropyl.

[0023] The term "alkyl" as employed herein refers to straight and branched chain aliphatic groups having from 1 to 12 carbon atoms, preferably 1-8 carbon atoms, and more preferably 1-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkyl groups include, without limitation, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl. A " C_0 " alkyl (as in " $\text{C}_0\text{-C}_3\text{-alkyl}$ ") is a covalent bond (like " C_0 " hydrocarbyl).

[0024] The term "alkenyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon double bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkenyl groups include, without limitation, ethenyl, propenyl, butenyl, pentenyl, and hexenyl.

[0025] The term "alkynyl" as used herein means an unsaturated straight or branched chain aliphatic group with one or more carbon-carbon triple bonds, having from 2 to 12 carbon atoms, preferably 2-8 carbon atoms, and more preferably 2-6 carbon atoms, which is optionally substituted with one, two or three substituents. Preferred alkynyl groups include, without limitation, ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0026] An "alkylene," "alkenylene," or "alkynylene" group is an alkyl, alkenyl, or alkynyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups. Preferred alkylene groups include, without limitation, methylene, ethylene, propylene, and butylene. Preferred alkenylene groups include, without limitation, ethenylene, propenylene, and butenylene. Preferred alkynylene groups include, without limitation, ethynylene, propynylene, and butynylene.

[0027] The term "cycloalkyl" as employed herein includes saturated and partially unsaturated cyclic hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons, wherein the cycloalkyl group additionally is optionally substituted. Preferred cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl.

[0028] The term "heteroalkyl" refers to an alkyl group, as defined hereinabove, wherein one or more carbon atoms in the chain are replaced by a heteroatom selected from the group consisting of O, S, and N.

[0029] An "aryl" group is a C₆-C₁₄ aromatic moiety comprising one to three aromatic rings, which is optionally substituted. Preferably, the aryl group is a C₆-C₁₀ aryl group. Preferred aryl groups include, without limitation, phenyl, naphthyl, anthracenyl, and fluorenyl. An "aralkyl" or "arylalkyl" group comprises an aryl group covalently linked to an alkyl group, either of which may independently be optionally substituted or unsubstituted. Preferably, the aralkyl group is (C₁-C₆)alk(C₆-C₁₀)aryl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0030] A "heterocyclyl" or "heterocyclic" group is a ring structure having from about 3 to about 8 atoms, wherein one or more atoms are selected from the group consisting of N, O, and S. The heterocyclic

group is optionally substituted on carbon at one or more positions. The heterocyclic group is also independently optionally substituted on nitrogen with alkyl, aryl, aralkyl, alkylcarbonyl, alkylsulfonyl, arylcarbonyl, arylsulfonyl, alkoxycarbonyl, aralkoxycarbonyl, or on sulfur with oxo or lower alkyl. Preferred heterocyclic groups include, without limitation, epoxy, aziridinyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, thiazolidinyl, oxazolidinyl, oxazolidinonyl, and morpholino. In certain preferred embodiments, the heterocyclic group is fused to an aryl, heteroaryl, or cycloalkyl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinoline and dihydrobenzofuran. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0031] As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to three heteroatoms per ring selected from the group consisting of N, O, and S. A "heteroaralkyl" or "heteroarylalkyl" group comprises a heteroaryl group covalently linked to an alkyl group, either of which is independently optionally substituted or unsubstituted. Preferred heteroaralkyl groups comprise a C₁-C₆ alkyl group and a heteroaryl group having 5, 6, 9, or 10 ring atoms. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms. Examples of preferred heteroaralkyl groups include pyridylmethyl, pyridylethyl, pyrrolylmethyl, pyrrolylethyl, imidazolylmethyl, imidazolylethyl, thiazolylmethyl, and thiazolylethyl. Specifically excluded from the scope of this term are compounds having adjacent annular O and/or S atoms.

[0032] An "arylene," "heteroarylene," or "heterocyclylene" group is an aryl, heteroaryl, or heterocyclyl group, as defined hereinabove, that is positioned between and serves to connect two other chemical groups.

[0033] Preferred heterocyclyls and heteroaryls include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl,

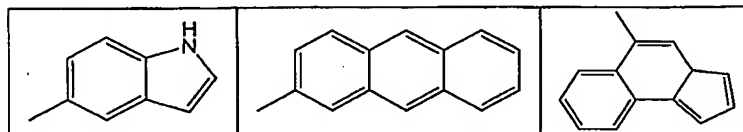
chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinoliziny, quinoxaliny, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

[0034] As employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-) nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

- (a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino,

- (b) C₁-C₅ alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, aryloxy, carbonyl, C₂-C₈ acyl, C₂-C₈ acylamino, C₁-C₈ alkylthio, arylalkylthio, arylthio, C₁-C₈ alkylsulfinyl, arylalkylsulfinyl, arylsulfinyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C₀-C₆ N-alkyl carbamoyl, C₂-C₁₅ N,N-dialkylcarbamoyl, C₃-C₇ cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C₃-C₇ heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocycle, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; and
- (c) -(CH₂)_s-NR³⁰R³¹, wherein s is from 0 (in which case the nitrogen is directly bonded to the moiety that is substituted) to 6, and R³⁰ and R³¹ are each independently hydrogen, cyano, oxo, carboxamido, amidino, C₁-C₈ hydroxyalkyl, C₁-C₃ alkylaryl, aryl-C₁-C₃ alkyl, C₁-C₈ alkyl, C₁-C₈ alkenyl, C₁-C₈ alkoxy, C₁-C₈ alkoxycarbonyl, aryloxy, carbonyl, aryl-C₁-C₃ alkoxycarbonyl, C₂-C₈ acyl, C₁-C₈ alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, aroyl, aryl, cycloalkyl, heterocycle, or heteroaryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above; or
- R³⁰ and R³¹ taken together with the N to which they are attached form a heterocycle or heteroaryl, each of which is optionally substituted with from 1 to 3 substituents from (a), above.

[0035] In addition, substituents on cyclic moieties (i.e., cycloalkyl, heterocycle, aryl, heteroaryl) include 5-6 membered mono- and 10-12 membered bi-cyclic moieties fused to the parent cyclic moiety to form a bi- or tri-cyclic fused ring system. For example, an optionally substituted phenyl includes the following:



[0036] A "halohydrocarbyl" is a hydrocarbyl moiety in which from one to all hydrogens have been replaced with one or more halo.

[0037] The term "halogen" or "halo" as employed herein refers to chlorine, bromine, fluorine, or iodine. As herein employed, the term "acyl" refers to an alkylcarbonyl or arylcarbonyl substituent. The term "acylamino" refers to an amide group attached at the nitrogen atom (i.e., R-CO-NH-). The term "carbamoyl" refers to an amide group attached at the carbonyl carbon atom (i.e., NH₂-CO-). The nitrogen atom of an acylamino or carbamoyl substituent is additionally substituted. The term "sulfonamido" refers to a sulfonamide substituent attached by either the sulfur or the nitrogen atom. The term "amino" is meant to include NH₂, alkylamino, arylamino, and cyclic amino groups. The term "ureido" as employed herein refers to a substituted or unsubstituted urea moiety.

[0038] The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons.

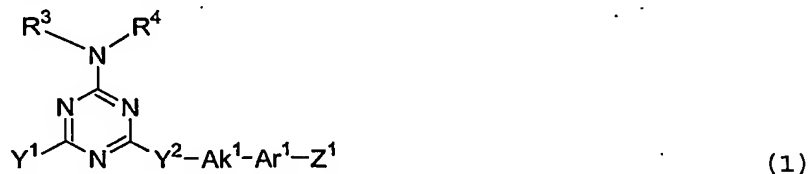
[0039] A moiety that is substituted is one in which one or more hydrogens have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-fluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2-fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyl-octyl. Included within this definition are methylenes (-CH₂-) substituted with oxygen to form carbonyl -CO-).

[0040] An "unsubstituted" moiety as defined above (e.g., unsubstituted cycloalkyl, unsubstituted heteroaryl, etc.) means that moiety as defined above that does not have any of the optional substituents for which the definition of the moiety (above) otherwise provides. Thus, for example, while an "aryl" includes phenyl and phenyl substituted with a halo, "unsubstituted aryl" does not include phenyl substituted with a halo.

[0041] Preferred embodiments of a particular genus of compounds of the invention include combinations of preferred embodiments. For example, paragraph [0043] identifies a preferred Ay¹ and paragraph [0047] identifies preferred Ar¹ (both for compound (1) of paragraph [0042]). Thus, another preferred embodiment includes those compounds of formula (1) in paragraph [0042] in which Ay¹ is as defined in paragraph [0043] and Ar¹ is as defined in paragraph [0047].

Compounds

[0042] In a first aspect, the invention provides novel inhibitors of histone deacetylase. In a first embodiment, the novel inhibitors of histone deacetylase are represented by formula (1):



and pharmaceutically acceptable salts thereof, wherein

R^3 and R^4 are independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and $-\text{L}^1 - \text{Cy}^1$, wherein

L^1 is $\text{C}_1 - \text{C}_6$ alkyl, $\text{C}_2 - \text{C}_6$ heteroalkyl, or $\text{C}_3 - \text{C}_6$ alkenyl; and

Cy^1 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

R^3 and R^4 are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally forms part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

Y^1 is selected from the group consisting of $-\text{N}(\text{R}^1)(\text{R}^2)$, $-\text{CH}_2 - \text{C}(\text{O}) - \text{N}(\text{R}^1)(\text{R}^2)$, halogen, and hydrogen, wherein

R^1 and R^2 are independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and $-\text{L}^1 - \text{Cy}^1$, wherein

L^1 is $\text{C}_1 - \text{C}_6$ alkyl, $\text{C}_2 - \text{C}_6$ heteroalkyl, or $\text{C}_3 - \text{C}_6$ alkenyl; and

Cy^1 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted; or

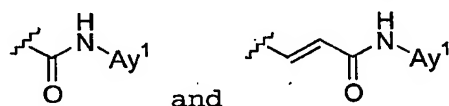
R^1 and R^2 are taken together with the adjacent nitrogen atom to form a 5-, 6-, or 7-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, S, and N, and wherein the ring optionally is substituted, and optionally may form part of a bicyclic ring system, or optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings and ring systems optionally is substituted;

Y^2 is a chemical bond or $N(R^0)$, where R^0 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl;

Ak^1 is C_1 - C_6 alkylene, C_1 - C_6 -heteroalkylene (preferably, in which one $-CH_2-$ is replaced with $-NH-$, and more preferably $-NH-CH_2-$), C_2 - C_6 alkenylene or C_2 - C_6 alkynylene;

Ar^1 is arylene or heteroarylene, either of which optionally is substituted; and

Z^1 is selected from the group consisting of



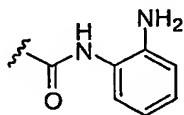
wherein Ay^1 is aryl or heteroaryl, which optionally is substituted.

[0043] Preferably in the compounds according to paragraph [0042], Ay^1 is phenyl or thienyl, each substituted with $-OH$ or $-NH_2$.

[0044] More preferably in the compounds according to paragraph [0042], Ay^1 is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay^2 is attached.

[0045] More preferably in the compounds according to paragraph [0042], Ay^1 is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

[0046] In some preferred embodiments of the compounds according to paragraph [0042], Z^1 is



[0047] In some preferred embodiments of the compounds according to paragraph [0042], Ar^1 is phenylene. In some embodiments, Ak^1 is

alkylene, preferably methylene. In some preferred embodiments, Y^2 is $-NH-$. In some preferred embodiments, Y^1 is $-N(R^1)(R^2)$ or $-CH_2-C(O)-N(R^1)(R^2)$.

[0048] In some embodiments of the compounds according to paragraph [0042], R^1 and R^2 are each independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and $-L^1-Cy^1$. In some embodiments, R^1 and/or R^2 is hydrogen. In other embodiments, R^1 and/or R^2 is alkyl or alkenyl, preferably allyl. In still other embodiments, R^1 and/or R^2 is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings. Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R^1 and/or R^2 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

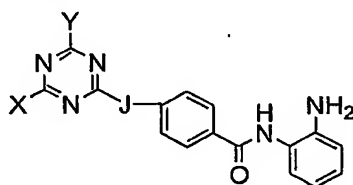
[0049] In some embodiments of the compounds according to paragraph [0042], R^3 and R^4 are each independently selected from the group consisting of hydrogen, L^1 , Cy^1 , and $-L^1-Cy^1$. In some embodiments, R^3 and/or R^4 is hydrogen. In other embodiments, R^3 and/or R^4 is alkyl or alkenyl, preferably allyl. In still other embodiments, R^3 and/or R^4 is aryl, heteroaryl, aralkyl, or heteroaralkyl, the rings of each of which optionally is substituted and optionally is fused to one or more aryl rings. Some preferred aryl, heteroaryl, aralkyl, and heteroaralkyl groups comprise a phenyl, pyridyl, or pyrrolyl ring. In still other embodiments, R^3 and/or R^4 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl, which optionally is substituted and optionally is fused to one or more aryl rings.

[0050] As set forth above, L^1 is C_1-C_6 alkyl, C_2-C_6 heteroalkyl, or C_3-C_6 alkenyl. However, one skilled in the art will understand that when L^1 is not a terminal group, then L^1 is C_1-C_6 alkylene, C_2-C_6 heteroalkylene, or C_3-C_6 alkenylene. In some embodiments, L^1 is alkylene, preferably methylene or ethylene. In other embodiments, L^1 is alkenyl, preferably allyl. In some embodiments, Cy^1 is the radical of a heterocyclic group including, without limitation, piperidine, pyrrolidine, piperazine, and morpholine, each of which optionally is substituted and optionally is fused to one or more aryl rings. In other embodiments Cy^1 is cycloalkyl, e.g., cyclopropyl, cyclopentyl, or cyclohexyl. In still other embodiments, Cy^1 is aryl or heteroaryl,

e.g., phenyl, pyridyl, or pyrrolyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy¹ is fused to one or two benzene rings. In some embodiments, Cy¹ has between one and about five substituents selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ alkoxy, and halo. Examples of preferred substituents include methyl, methoxy, and fluoro.

[0051] In some embodiments of the compounds according to paragraph [0042], R¹ and R² and/or R³ and R⁴ are taken together with the adjacent nitrogen atom to form a 5- or 6-membered ring, wherein the ring atoms are independently selected from the group consisting of C, O, and N, and wherein the ring optionally is substituted, and optionally is fused to one or more aryl rings. In some preferred embodiments, R¹ and R² and/or R³ and R⁴ are taken together with the adjacent nitrogen atom to form a ring such as, for example, pyrrolidine, piperidine, piperazine, and morpholine, wherein the ring optionally is substituted, and optionally is fused to an aryl ring. In some embodiments, the ring comprising R¹ and R² or R³ and R⁴ is fused to a benzene ring. In some embodiments, the ring comprising R¹ and R² or R³ and R⁴ has a substituent comprising an aryl or cycloalkyl ring, either of which optionally is substituted and optionally is fused to a cycloalkyl, aryl, heteroaryl, or heterocyclic ring. Preferred substituents include, without limitation, phenyl, phenylmethyl, and phenylethyl, the phenyl ring of which optionally is fused to a cycloalkyl, aryl, or heterocyclic ring.

[0052] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of formula 1(a):



(1a)

and pharmaceutically acceptable salts thereof, wherein

J is C₁-C₃-hydrocarbyl, -N(R²⁰)-, -N(R²⁰)-CH₂-, -O-, or -O-CH₂-;

R²⁰ is -H or -Me;

X and Y are independently selected from -NH₂, cycloalkyl, heterocyclyl, aryl, heteroaryl, and A-(C₁-C₆-alkyl)_n-B-;

A is H, C₁-C₆-alkyloxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

B is -NH-, -O-, or a direct bond; and

n is 0 (in which case A is directly bonded to B) or 1.

[0053] Preferably in the compounds according to paragraph [0052], A is phenyl optionally substituted with one or more moieties selected from halo (preferably chloro) and methoxy, and B is -NH-. In another preferred embodiment, A is selected from cyclopropyl, pyridinyl, and indanyl.

[0054] Preferably in the compounds according to paragraph [0052], J is -NH-CH₂-, -O-CH₂-, -N(CH₃)-CH₂-, -CH=CH-, or -CH₂-CH₂-.

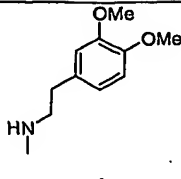
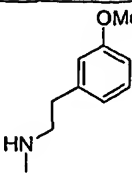
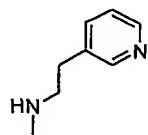

[0055] Preferably in the compounds according to paragraph [0052], R²⁰ is -H.

[0056] In the compounds according to paragraph [0052] X is preferably selected from

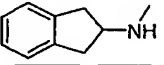

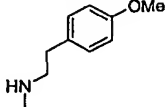
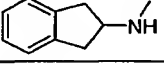

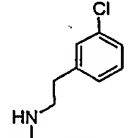
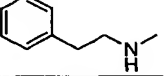

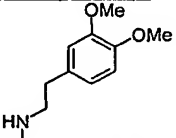

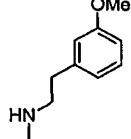
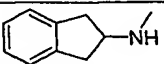

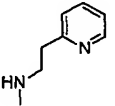
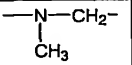
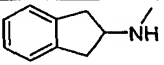

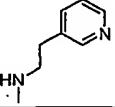
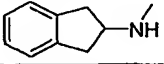
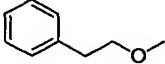

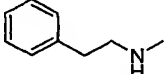


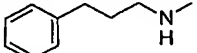
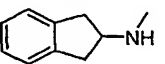

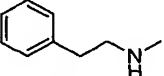

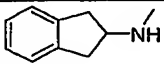
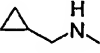
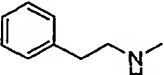
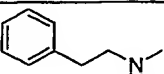

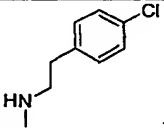
| | | | |
|-----|------------------|-------|--|
| | | | |
| | | -OMe, | |
| | -NH ₂ | | |
| | | | |
| and | | | |

and Y is preferably selected from

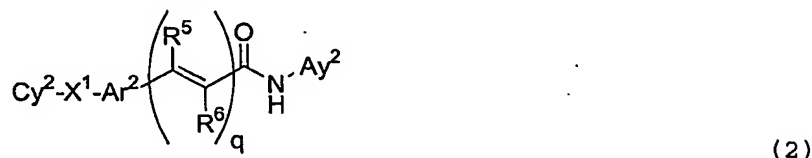
| | | | |
|---------------------------------------|--|--|---------|
| -NH ₂ , | | | n-BuNH, |
| MeOCH ₂ CH ₂ NH | | | |

| | | | |
|---|---|---|---|
|  |  |  |  |
| -H | Me | -OMe | $\text{CH}_3(\text{CH}_2)_3\text{N}$ H- |
| and | $\text{CH}_3\text{O}(\text{CH}_2)_2\text{-NH-}$ | | |

[0057] In a more preferred embodiment of the compounds according to paragraph [0052], the HDAC inhibitors of the invention comprise the following compounds of formula 1a:

| Cpd | J | X | Y | Cpd | J | X | Y |
|-----|---|---|---|-----|----------------------|---|---|
| 204 | -NH- |  | -NH ₂ | 476 | -NHCH ₂ - |  |  |
| 207 | -OCH ₂ - |  | -NH ₂ | 477 | -NHCH ₂ - |  |  |
| 210 | -NHCH ₂ - |  | -H | 478 | -NHCH ₂ - |  |  |
| 212 | -NHCH ₂ - | -OMe | -OMe | 479 | -NHCH ₂ - |  |  |
| 214 | -NHCH ₂ - |  | -OMe | 480 | -NHCH ₂ - |  |  |
| 216 |  |  | -Me | 481 | -NHCH ₂ - |  |  |
| 218 | -NHCH ₂ - |  | -Me | 482 | -NHCH ₂ - |  |  |
| 220 | -CH=CH- | -NH ₂ | -NH ₂ - | 483 | -NHCH ₂ - |  | Me |
| 223 | -CH=CH- |  | -NH ₂ | 484 | -NHCH ₂ - |  | NH ₂ |
| 224 | -CH ₂ CH ₂ - | -NH ₂ | -NH ₂ | and | | | |
| 470 | -NHCH ₂ - |  | NH ₂ | 485 | -NHCH ₂ - |  |  |
| 471 | -NHCH ₂ - |  |  | | | | |
| 472 | -NHCH ₂ - |  |  | | | | |
| 473 | -NHCH ₂ - |  | n-BuNH | | | | |
| 474 | -NHCH ₂ - |  | MeO(CH ₂) ₃ NH | | | | |
| 475 | -NHCH ₂ - |  |  | | | | |

[0058] In a second aspect, the novel histone deacetylase inhibitors of the invention are represented by formula (2):



and pharmaceutically acceptable salts thereof, wherein.

Cy^2 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which is optionally substituted and each of which is optionally fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings is optionally substituted;

X^1 is selected from the group consisting of a covalent bond, $\text{M}^1\text{-L}^2\text{-M}^1$, and $\text{L}^2\text{-M}^2\text{-L}^2$ wherein

L^2 , at each occurrence, is independently selected from the group consisting of a chemical bond, $\text{C}_0\text{-C}_4$ hydrocarbyl, $\text{C}_0\text{-C}_4\text{-hydrocarbyl-(NH)-C}_0\text{-C}_4\text{-hydrocarbyl}$, $\text{C}_0\text{-C}_4\text{-hydrocarbyl-(S)-C}_0\text{-C}_4\text{-hydrocarbyl}$, and $\text{C}_0\text{-C}_4\text{-hydrocarbyl-(O)-C}_0\text{-C}_4\text{-hydrocarbyl}$, provided that L^2 is not a chemical bond when X^1 is $\text{M}^1\text{-L}^2\text{-M}^1$;

M^1 , at each occurrence, is independently selected from the group consisting of -O- , $\text{-N(R}^7\text{)-}$, -S- , -S(O)- , $\text{S(O)}_2\text{-}$, $\text{-S(O)}_2\text{N(R}^7\text{)-}$, $\text{-N(R}^7\text{)-S(O)}_2\text{-}$, -C(O)- , -C(O)-NH- , -NH-C(O)- , -NH-C(O)-O- and -O-C(O)-NH- , wherein R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, acyl, heterocyclyl, and heteroaryl; and

M^2 is selected from the group consisting of M^1 , heteroarylene, and heterocyclylene, either of which rings optionally is substituted;

Ar^2 is arylene or heteroarylene, each of which is optionally substituted;

R^5 and R^6 are independently selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl;

q is 0 or 1; and

Ay^2 is a 5-6 membered cycloalkyl, heterocyclyl, or heteroaryl substituted with an amino or hydroxy moiety (preferably these groups are ortho to the amide nitrogen to which Ay^2 is attached) and further optionally substituted;

provided that when Cy² is naphthyl, X¹ is -CH₂-, Ar² is phenyl, R⁵ and R⁶ are H, and q is 0 or 1, Ay² is not phenyl or o-hydroxyphenyl.

[0059] In a preferred embodiment of the compounds according to paragraph [0058], when Ay² is o-phenol optionally substituted by halo, nitro, or methyl, Ar² is optionally substituted phenyl, X¹ is -O-, -CH₂-, -S-, -S-CH₂-, -S(O)-, -S(O)₂-, -C(O)-, or -OCH₂-, then Cy² is not optionally substituted phenyl or naphthyl.

[0060] In another preferred embodiment of the compounds according to paragraph [0058], when Ay² is o-anilinyll optionally substituted by halo, C₁-C₆-alkyl, C₁-C₆-alkoxy or -NO₂, q is 0, Ar² is phenyl, and X¹ is -CH₂-, then Cy² is not substituted pyridone (which substituents of the pyridone are not limited to substituents described herein).

[0061] In another preferred embodiment of the compounds according to paragraph [0058], when X¹ is -CH₂-, Ar² is optionally substituted phenyl, q is 1, and R⁶ is H, then Cy² is not optionally substituted imidazole.

[0062] In another preferred embodiment of the compounds according to paragraph [0058], when Ar² is amino or hydroxy substituted phenyl, X¹ is C₀-C₈-alkyl-X^{1a}- C₀-C₈-alkyl, wherein X^{1a} is -CH₂-, -O-, -S-, -NH-, -C(O)-, then Cy² is not optionally substituted naphthyl or di- or -tetrahydronaphthalene.

[0063] In another preferred embodiment of the compounds according to paragraph [0058], when Ay² is o-phenol, Ar² is substituted phenyl, X¹ is -O-, -S-, -CH₂-, -O-CH₂-, -S-CH₂-, or -C(O)-, and R⁵ and R⁶ are H, then Cy² is not optionally substituted naphthyl.

[0064] In another preferred embodiment of the compounds according to paragraph [0058], when Ay² is o-anilinyll, q is 0, Ar² is unsubstituted phenyl, X¹ is -CH₂-, then Cy² is not substituted 6-hydroimidazolo[5,4-d]pyridazin-7-one-1-yl or substituted 6-hydroimidazolo[5,4-d]pyridazine-7-thione-1-yl.

[0065] Preferably in the compounds according to paragraph [0058], Ay² is phenyl or thienyl, each substituted with -OH or -NH₂.

[0066] More preferably in the compounds according to paragraph [0058], Ay² is optionally amino- or hydroxy-substituted phenyl or thienyl, wherein the amino or hydroxy substituent is preferably ortho to the nitrogen to which Ay² is attached.

[0067] More preferably in the compounds according to paragraph [0058], Ay^2 is ortho aniline, ortho phenol, 3-amino-2-thienyl, or 3-hydroxy-2-thienyl, and tautomers thereof.

[0068] In another embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0058] wherein

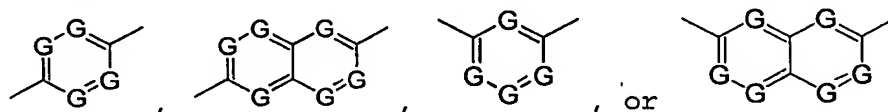
q is 1;

M^1 , at each occurrence, is selected from the group consisting of $-N(R^7)-$, $-S-$, $-C(O)-NH-$, and $-O-C(O)-NH-$, where R^7 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, and acyl; and

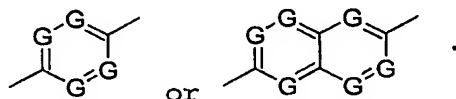
Ay^2 is anilinyll, which optionally is substituted.

[0069] In some preferred embodiments of the compounds according to paragraph [0068], the $-NH_2$ group of Ay^2 is in an ortho position with respect to the nitrogen atom to which Ay^2 is attached. In some embodiments, R^5 and R^6 are independently selected from the group consisting of hydrogen and C_1-C_4 alkyl. In some preferred embodiments, R^5 and R^6 are hydrogen.

[0070] In some embodiments of the compounds according to paragraph [0068], Ar^2 has the formula



wherein G , at each occurrence, is independently N or C , and C optionally is substituted. In some preferred embodiments, Ar^2 has the formula

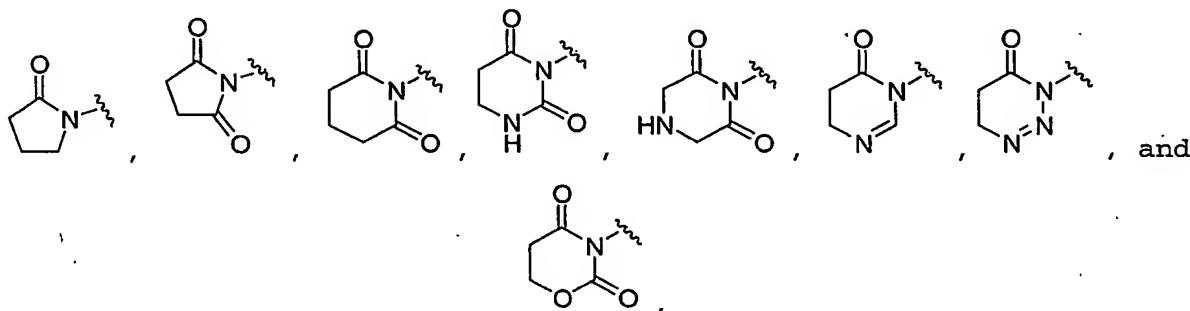


[0071] In some preferred embodiments of the compounds according to paragraph [0070], Ar^2 is selected from the group consisting of phenylene, pyridylene, pyrimidylene, and quinolyne.

[0072] In some embodiments of the compounds according to paragraph [0068], X^1 is a chemical bond. In some embodiments, X^1 is $L^2-M^2-L^2$, and M^2 is selected from the group consisting of $-NH-$, $-N(CH_3)-$, $-S-$, $-C(O)-N(H)-$, and $-O-C(O)-N(H)-$. In some embodiments, X^1 is $L^2-M^2-L^2$, where at least one occurrence of L^2 is a chemical bond. In other embodiments, X^1 is $L^2-M^2-L^2$, where at least one occurrence of L^2 is alkylene, preferably methylene. In still other embodiments, X^1 is L^2-

M^2-L^2 , where at least one occurrence of L^2 is alkenylene. In some embodiments, X^1 is $M^1-L^2-M^1$ and M^1 is selected from the group consisting of $-NH-$, $-N(CH_3)-$, $-S-$, and $-C(O)-N(H)-$.

[0073] In some embodiments of the compounds according to paragraph [0068], Cy^2 is aryl or heteroaryl, e.g., phenyl, pyridyl, imidazolyl, or quinolyl, each of which optionally is substituted. In some embodiments, Cy^2 is heterocyclyl, e.g.,



each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, Cy^2 has from one and three substituents independently selected from the group consisting of alkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, trifluoromethoxy, nitro, amino, aminomethyl, and hydroxymethyl.

[0074] In a preferred embodiment of the compounds of paragraph [0058], the invention comprises compounds of structural formula (2a):



and pharmaceutically acceptable salts thereof, wherein

Ar^a is phenyl or thienyl;

R^6 is H, or C_1-C_6 -alkyl (preferably $-CH_3$);

Y and Z are independently $-CH=$ or $-N=$;

W is halo, $(V'-L^4)_t-V-L^3-$;

L^3 is a direct bond, $-C_1-C_6$ -hydrocarbyl, $-(C_1-C_3$ -hydrocarbyl) $_{m1}-$
 $X'-(C_1-C_3$ -hydrocarbyl) $_{m2}$, $-NH-(C_0-C_3$ -hydrocarbyl), $(C_1-C_3$ -
hydrocarbyl)- $NH-$, or $-NH-(C_1-C_3$ -hydrocarbyl)- $NH-$;

m_1 and m_2 are independently 0 or 1;

X' is $-N(R^{21})-$, $-C(O)N(R^{21})-$, $N(R^{21})C(O)-$, $-O-$, or $-S-$;

R^{21} is $-H$, $V''-(C_1-C_6$ -hydrocarbyl) $_c$;

L^4 is $(C_1-C_6\text{-hydrocarbyl})_a\text{-M-}(C_1-C_6\text{-hydrocarbyl})_b$;

a and b are independently 0 or 1;

M is $-\text{NH}-$, $-\text{NHC(O)}-$, $-\text{C(O)NH}-$, $-\text{C(O)}-$, $-\text{SO}_2-$, $-\text{NHSO}_2-$, or $-\text{SO}_2\text{NH}-$

V, V', and V'' are independently selected from cycloalkyl, heterocyclyl, aryl, and heteroaryl;

t is 0 or 1;

or W, the annular C to which it is bound, and Y together form a monocyclic cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

wherein the A and Ar^a rings are optionally further substituted with from 1 to 3 substituents independently selected from methyl, hydroxy, methoxy, halo, and amino.

[0075] In a preferred embodiment of the compound according to paragraph [0074]:

Y and Z are $-\text{CH=}$ and R^6 is H;

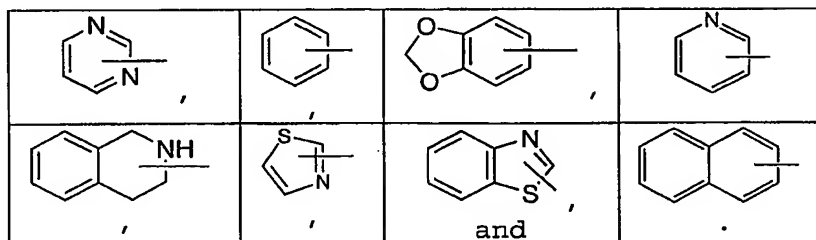
W is V-L^3 ;

L^3 is $-\text{NH-CH-}$ or $-\text{CH-NH-}$;

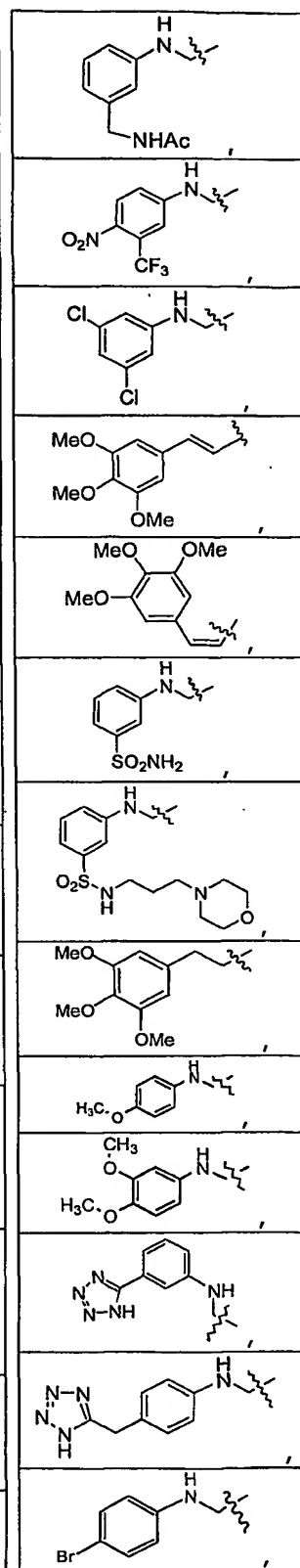
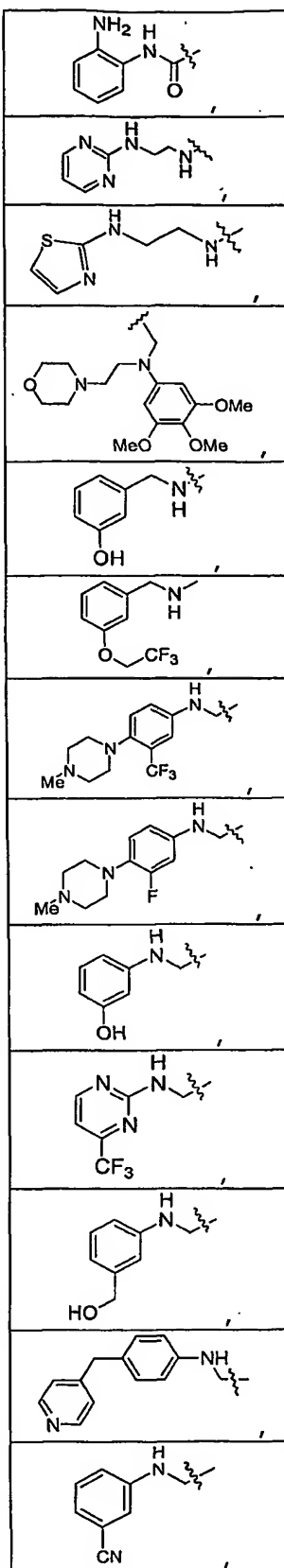
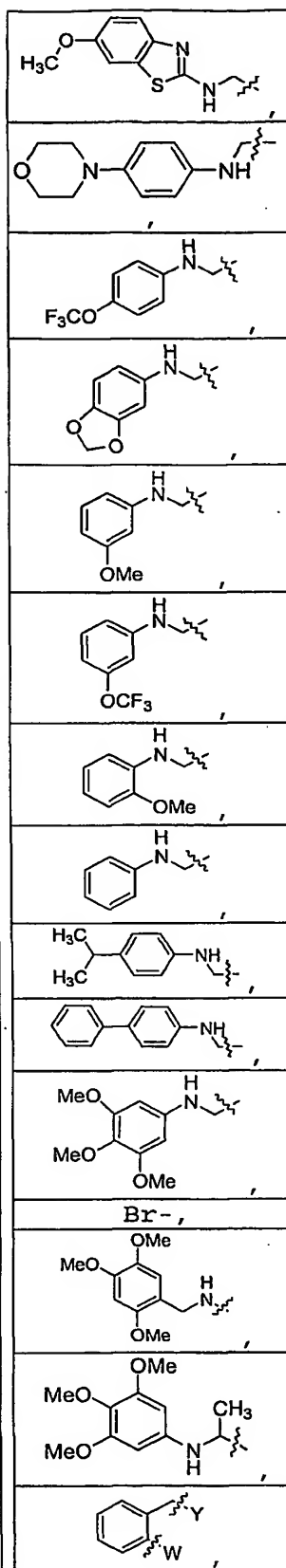
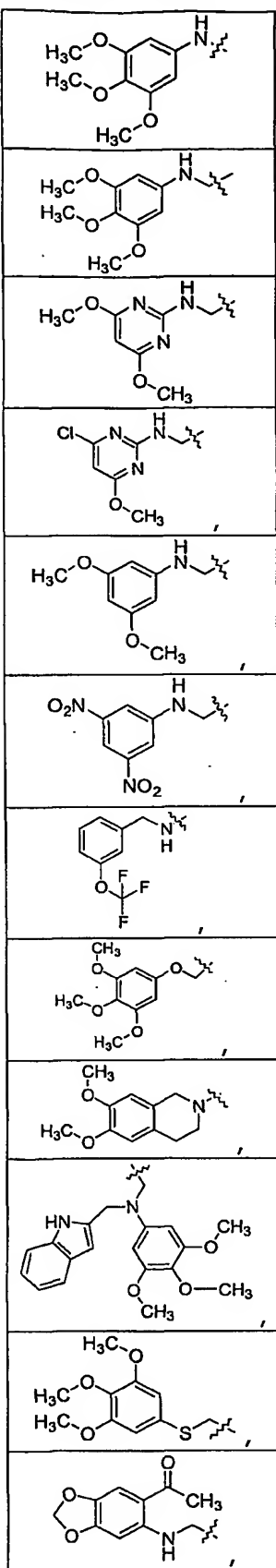
V is phenyl optionally substituted with from 1 to 3 moieties independently selected from halo, hydroxy, $\text{C}_1\text{-C}_6\text{-hydrocarbyl}$, $\text{C}_1\text{-C}_6\text{-hydrocarbyl-oxy}$ or $-\text{thio}$ (particularly methoxy or methylthio), wherein each of the hydrocarbyl moieties are optionally substituted with one or more moieties independently selected from halo, nitroso, amino, sulfonamido, and cyano; and

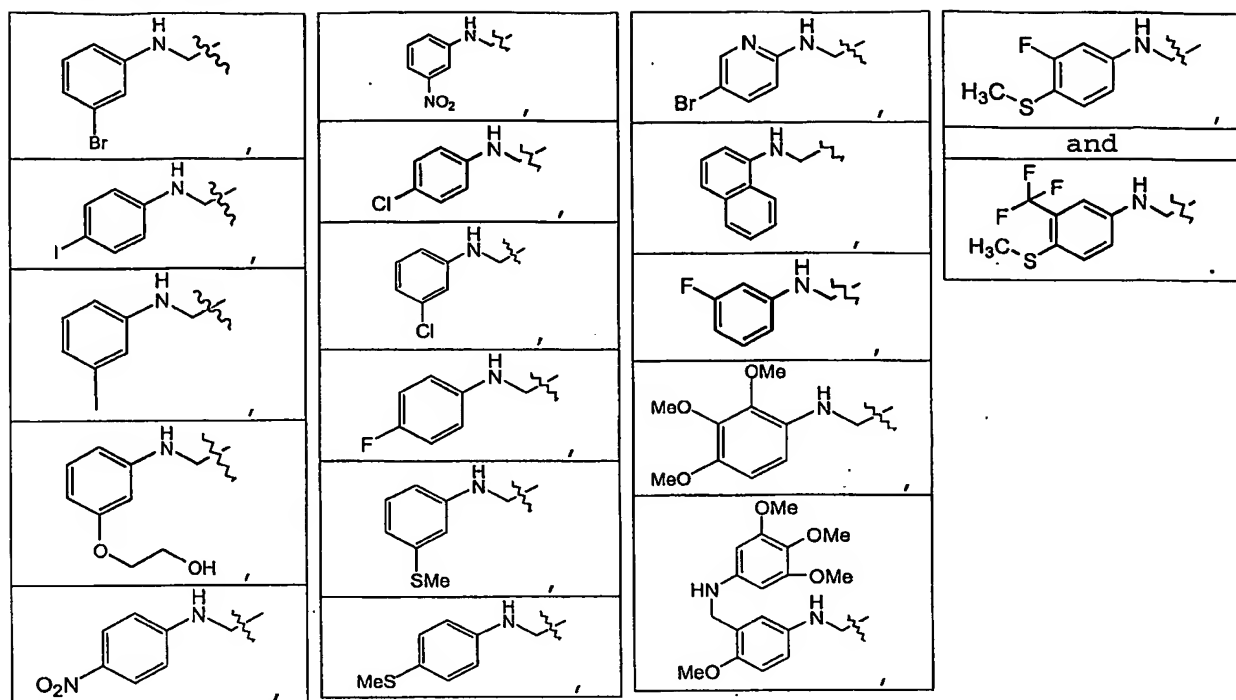
Ar^a is phenyl and the amino moieties to which it is bound are ortho to each other.

[0076] In some preferred embodiments of the compound according to paragraph [0074], V is an optionally substituted ring moiety selected from:



[0077] In another preferred embodiment of the compounds according to paragraph [0074], W is selected from:





[0078] In another preferred embodiment of the compounds according to paragraph [0074], the A and Ar^a rings are not further substituted.

[0079] In a particularly preferred embodiment of the compounds according to paragraph [0074], the compounds of the invention are selected from the following, in which, unless expressly displayed otherwise, Ar^a is phenyl (and, preferably, the amide nitrogen and the amino nitrogen bound to Ar^a are *ortho* to each other):

| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 481 | | CH | CH | H |
| 484 | | | | |
| 492 | | CH | CH | H |
| 493 | | CH | CH | H |

| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 494 | | CH | CH | H |
| 495 | | CH | CH | H |
| 496 | | CH | CH | H |
| 497 | | CH | CH | H |

| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 498 | | CH | CH | H |
| 499 | | CH | CH | H |
| 500 | | CH | CH | H |
| 501 | | CH | CH | H |
| 502 | | CH | CH | H |
| 503 | | CH | CH | H |
| 504 | | CH | CH | H |
| 505 | | CH | CH | H |
| 506 | | CH | CH | H |
| 507 | | CH | CH | H |
| 508 | | CH | CH | H |
| 509 | | CH | CH | H |
| 510 | | CH | CH | H |
| 511 | | CH | CH | H |

| Cpd | W | Y | Z | R ⁶ |
|-----|------|----|----|-----------------|
| 512 | | CH | N | H |
| 516 | Br - | CH | CH | CH ₃ |
| 517 | | CH | CH | CH ₃ |
| 518 | | CH | CH | CH ₃ |
| 519 | | CH | CH | H |
| 520 | | CH | CH | H |
| 521 | | N | CH | H |
| 522 | | N | CH | H |
| 523 | | CH | CH | H |
| 524 | | N | CH | H |
| 525 | | N | CH | H |
| 526 | | CH | CH | H |
| 527 | | CH | CH | H |
| 528 | | CH | CH | H |
| 529 | | CH | CH | H |

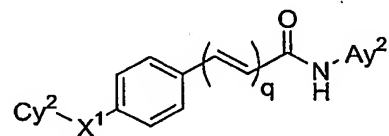
| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 530 | | CH | CH | H |
| 531 | | CH | CH | H |
| 532 | | CH | CH | H |
| 533 | | CH | CH | H |
| 534 | | CH | CH | H |
| 535 | | CH | CH | H |
| 536 | | CH | CH | H |
| 537 | | CH | CH | H |
| 538 | | CH | CH | H |
| 539 | | CH | CH | H |
| 540 | | CH | CH | H |
| 541 | | CH | CH | H |
| 542 | | CH | CH | H |

| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 543 | | CH | CH | H |
| 544 | | CH | CH | H |
| 545 | | CH | CH | H |
| 546 | | CH | CH | H |
| 547 | | CH | CH | H |
| 548 | | CH | CH | H |
| 549 | | CH | CH | H |
| 550 | | CH | CH | H |
| 551 | | CH | CH | H |
| 552 | | CH | CH | H |
| 553 | | CH | CH | H |
| 554 | | CH | CH | H |
| 555 | | CH | CH | H |

| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 556 | | CH | CH | H |
| 557 | | CH | CH | H |
| 558 | | CH | CH | H |
| 559 | | CH | CH | H |
| 560 | | | | |
| 561 | | | | |
| 562 | | CH | CH | H |
| 563 | | CH | CH | H |

| Cpd | W | Y | Z | R ⁶ |
|-----|---|----|----|----------------|
| 564 | | | | |
| 565 | | CH | CH | H |
| 566 | | CH | CH | H |
| 567 | | | | |
| 568 | | | | |
| 569 | | CH | N | H |
| 570 | | | | |

[0080] In a preferred embodiment, the compounds of the invention comprise compounds of the formula (2b):



(2b)

and pharmaceutically acceptable salts thereof, wherein

Ay² is phenyl or thienyl, each substituted at the ortho position with -NH₂ or -OH and each further optionally substituted with one to three substituents independently selected from -NH₂, -OH, and halo;

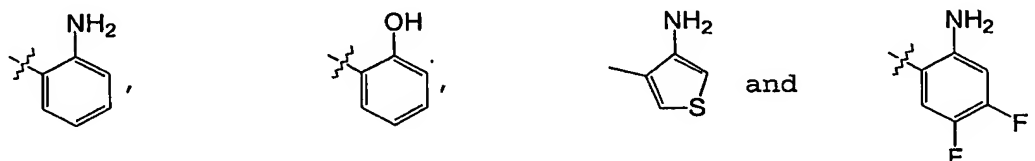
q is 0 or 1;

X^1 is selected from $-\text{CH}_2-$, $-\text{NH}-\text{CH}_2-$, and $-\text{S}-\text{CH}_2-$;

Cy^2 is monocyclic or fused bicyclic aryl or heteroaryl optionally substituted with one to three substituents selected from CH_3- , $\text{CH}_3\text{O}-$, phenyl optionally substituted with one to three $\text{CH}_3\text{O}-$, morpholinyl, morpholinyl- C_1-C_3 -alkoxy, cyano, and $\text{CH}_3\text{C}(\text{O})\text{NH}-$;

provided that when Cy^2 is naphthyl, X^1 is $-\text{CH}_2-$, and q is 0 or 1, Ay^2 is not *o*-hydroxyphenyl.

[0081] Preferably in the compounds according to paragraph [0080], Ay^2 is selected from:



[0082] Preferably in the compounds according to paragraph [0080], Cy^2 is phenyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, thienyl, tetrahydroquinazolinyl, or 1,3-dihydroquinazoline-2,4-dione, each optionally substituted with one to three $\text{CH}_3\text{O}-$. More preferably, Cy^2 is phenyl substituted with one to three $\text{CH}_3\text{O}-$.

[0083] In a third embodiment, the novel inhibitors of histone deacetylase are represented by formula (3):



and pharmaceutical salts thereof, wherein

Ar^3 is arylene or heteroarylene, either of which optionally is substituted;

Cy^3 is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings, each of which rings optionally is substituted;

provided that when Cy^3 is a cyclic moiety having $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$ in the ring, then Cy^3 is not additionally substituted with a group comprising an aryl or heteroaryl ring; and

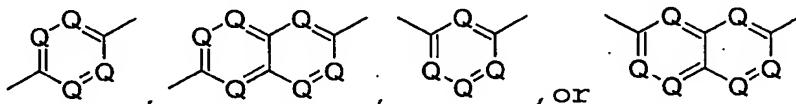
X^2 is selected from the group consisting of a chemical bond, L^3 , W^1-L^3 , L^3-W^1 , $\text{W}^1-\text{L}^3-\text{W}^1$, and $\text{L}^3-\text{W}^1-\text{L}^3$, wherein

W^1 , at each occurrence, is S, O, or $N(R^9)$, where R^9 is selected from the group consisting of hydrogen, alkyl, aryl, and aralkyl; and

L^3 is C_1 - C_4 alkylene, C_2 - C_4 alkenylene, or C_2 - C_4 alkynylene; provided that X^2 does not comprise a $-C(O)-$, $-C(S)-$, $-S(O)-$, or $-S(O)_2-$ group;

and further provided that when Cy^3 is pyridine, then X^2 is L^3 , W^1-L^3 , or L^3-W^1 .

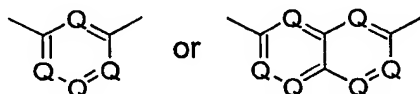
[0084] Preferably, Ar^3 has the structure:



wherein Q, at each occurrence, is independently N or C, and C optionally is substituted.

[0085] Preferably in the compounds according to paragraph [0083], X^2 is selected from the group consisting of L^3 , W^1-L^3 , L^3-W^1 , $W^1-L^3-W^1$, and $L^3-W^1-L^3$.

[0086] Preferably in the compounds according to paragraph [0083], when X^2 is a chemical bond, then Ar^3 is not



and Cy^3 is not the radical of a substituted or unsubstituted diazepine or benzofuran.

[0087] In some embodiments of the compounds according to paragraph [0083], Q at each occurrence is $C(R^8)$, where R^8 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, alkoxy, amino, nitro, halo, haloalkyl, and haloalkoxy. In some other embodiments, from one to about three variables Q are nitrogen. In some preferred embodiments, Ar^3 is selected from the group consisting of phenylene, pyridylene, thiazolylenes, and quinolylenes.

[0088] In some embodiments of the compounds according to paragraph [0083], X^2 is a chemical bond. In other embodiments, X^2 is a non-cyclic hydrocarbyl. In some such embodiments, X^2 is alkylene, preferably methylene or ethylene. In other such embodiments, X^2 is alkenylene or alkynylene. In still other such embodiments, one carbon in the hydrocarbyl chain is replaced with $-NH-$ or $-S-$. In some preferred embodiments, X^2 is $W^1-L^3-W^1$ and W^1 is $-NH-$ or $-N(CH_3)-$.

[0089] In some embodiments of the compounds according to paragraph [0083], Cy³ is cycloalkyl, preferably cyclohexyl. In other embodiments, Cy³ is aryl or heteroaryl, e.g., phenyl, pyridyl, pyrimidyl, imidazolyl, thiazolyl, oxadiazolyl, quinolyl, or fluorenyl, each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the cyclic moiety of Cy³ is fused to a benzene ring. In some embodiments, Cy³ has from one to three substituents independently selected from the group consisting of alkyl, alkoxy, aryl, aralkyl, amino, halo, haloalkyl, and hydroxyalkyl. Examples of preferred substituents include methyl, methoxy, fluoro, trifluoromethyl, amino, nitro, aminomethyl, hydroxymethyl, and phenyl. Some other preferred substituents have the formula -K¹-N(H)(R¹⁰), wherein

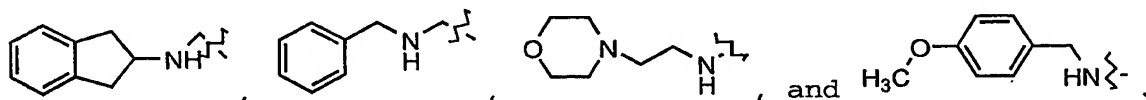
K¹ is a chemical bond or C₁-C₄ alkylene;

R^{10} is selected from the group consisting of Z' and $-Ak^2-Z'$,
wherein

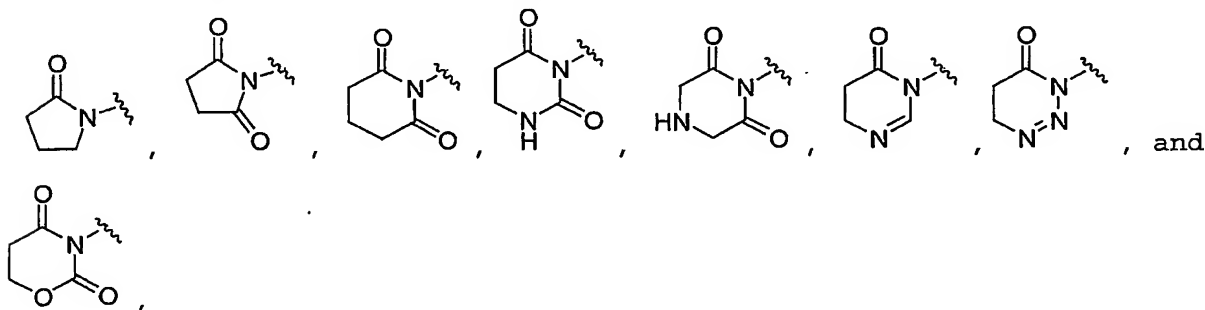
Ak² is C₁-C₄ alkylene; and

Z' is cycloalkyl, aryl, heteroaryl, or heterocyclyl, each of which optionally is substituted, and each of which optionally is fused to one or more aryl or heteroaryl rings, or to one or more saturated or partially unsaturated cycloalkyl or heterocyclic rings.

[0090] Examples of such preferred substituents according to paragraph
[0089] include



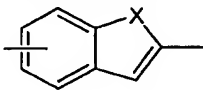
[0091] In some embodiments of the compounds according to paragraph [0083], Cy³ is heterocyclcyl, e.g.,



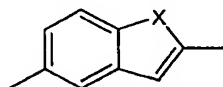
each of which optionally is substituted and optionally is fused to one or more aryl rings. In some embodiments, the heterocycle of Cy³ is fused to a benzene ring.

[0092] Preferably in the compounds of paragraph [0083], when Ar⁴ is quinoxalinylenes, then X³ is not -CH(OH)-.

[0093] In another preferred embodiment, Ar³ is



wherein X is -CH₂-, -NH-, O, or S. Preferably Ar³ is



and X is S or O.

[0094] In a preferred embodiment, the novel histone deacetylase inhibitors of the invention are those according to paragraph [0058] wherein

Ay² is ortho-anilinylnyl;

q is 0; and

X¹ is M¹-L²-M¹ or L²-M²-L².

[0095] In a preferred embodiment of the compounds according to paragraph [0094], Ar² is aryl or heteroaryl; and Cy²-X¹- is collectively selected from the group consisting of

- a) A₁-L₁-B₁-, wherein A₁ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₁ is -(CH₂)₀₋₁NH(CH₂)₀₋₁-, -NHC(O)-, or -NHCH₂-; and wherein B₁ is phenyl or a covalent bond;
- b) A₂-L₂-B₂-, wherein A₂ is CH₃(C=CH₂)-, optionally substituted cycloalkyl, optionally substituted alkyl, or optionally substituted aryl; wherein L₂ is -C≡C-; and wherein B₂ is a covalent bond;
- c) A₃-L₃-B₃-, wherein A₃ is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L₃ is a covalent bond; and wherein B₃ is -CH₂NH-;
- d) A₄-L₄-B₄-, wherein A₄ is an optionally substituted aryl; wherein L₄ is -NHCH₂-; and wherein B₄ is a thienyl group;

- e) $A_5-L_5-B_5-$, wherein A_5 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_5 is a covalent bond; and wherein B_5 is $-SCH_2-$;
- f) morpholinyl- CH_2-
- g) optionally substituted aryl;
- h) $A_6-L_6-B_6-$, wherein A_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_6 is a covalent bond; and wherein B_6 is $-NHCH_2-$;
- i) $A_7-L_7-B_7-$, wherein A_7 is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_7 is a covalent bond; and wherein B_7 is $-CH_2-$;
- j) optionally substituted heteroaryl or optionally substituted heterocyclyl;
- k) $A_8-L_8-B_8-$, wherein A_8 is optionally substituted phenyl; wherein L_8 is a covalent bond; and wherein B_8 is $-O-$;
- l) $A_9-L_9-B_9-$, wherein A_9 is an optionally substituted aryl; wherein L_9 is a covalent bond; and wherein B_9 is a furan group;
- m) $A_{10}-L_{10}-B_{10}-$, wherein A_{10} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{10} is $-CH(CH_2CH_3)-$; and wherein B_{10} is $-NHCH_2-$;
- n) $A_{11}-L_{11}-B_{11}-$, wherein A_{11} is an optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{11} is a covalent bond; and wherein B_{11} is $-OCH_2-$;
- o) $A_{12}-L_{12}-B_{12}-$, wherein A_{12} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{12} is $-NHC(O)-$; and wherein B_{12} is $-N(\text{optionally substituted aryl})CH_2-$;
- p) $A_{13}-L_{13}-B_{13}-$, wherein A_{13} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{13} is a covalent bond; and wherein B_{13} is $-NHC(O)-$;
- q) $A_{14}-L_{14}-B_{14}-$, wherein A_{14} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{14} is $-NHC(O)(\text{optionally substituted heteroaryl})-$; and wherein B_{14} is $-S-S-$;
- r) $F_3CC(O)NH-$;

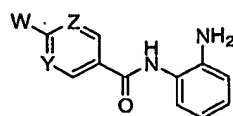
- s) $A_{15}-L_{15}-B_{15}-$, wherein A_{15} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{15} is $-(CH_2)_{0-1}NH$ (optionally substituted heteroaryl)-; and wherein B_{15} is $-NHCH_2-$;
- t) $A_{16}-L_{16}-B_{16}-$, wherein A_{16} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{16} is a covalent bond; and wherein B_{16} is $-N$ (optionally substituted alkyl) CH_2- ; and
- u) $A_{16}-L_{16}-B_{16}-$, wherein A_{16} is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein L_{16} is a covalent bond; and wherein B_{16} is $-(\text{optionally substituted aryl}-CH_2)_2-N-$.

[0096] In another preferred embodiment of the compounds according to paragraph [0094], Cy^2-X^1- is collectively selected from the group consisting of

- a) $D_1-E_1-F_1-$, wherein D_1 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_1 is $-CH_2-$ or a covalent bond; and wherein B_1 is a covalent bond;
- b) $D_2-E_2-F_2-$, wherein D_2 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_2 is $-NH(CH_2)_{0-2}-$; and wherein F_2 is a covalent bond;
- c) $D_3-E_3-F_3-$, wherein D_3 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_3 is $-(CH_2)_{0-2}NH-$; and wherein F_3 is a covalent bond;
- d) $D_4-E_4-F_4-$, wherein D_4 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_4 is $-S(CH_2)_{0-2}-$; and wherein F_4 is a covalent bond;
- e) $D_5-E_5-F_5-$, wherein D_5 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted heterocyclyl; wherein E_5 is $-(CH_2)_{0-2}S-$; and wherein F_5 is a covalent bond; and
- f) $D_6-E_6-F_6-$, wherein D_6 is an optionally substituted aryl, optionally substituted heteroaryl or optionally substituted

heterocyclyl; wherein E_6 is $-NH(CH_2)_{0-2}NH-$; and wherein F_6 is a covalent bond.

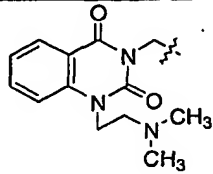
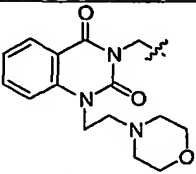
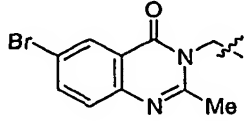
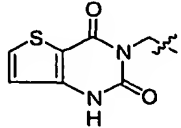
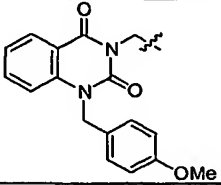
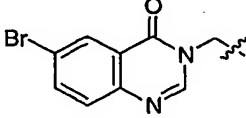
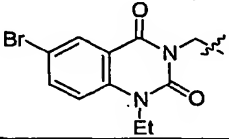
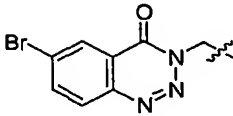
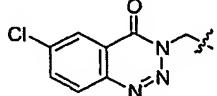
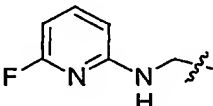
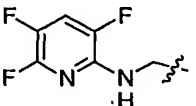
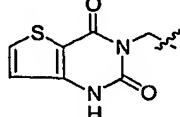
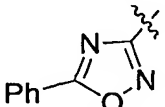
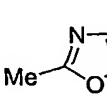
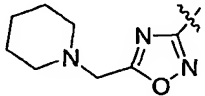
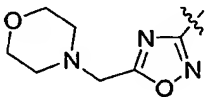
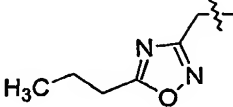
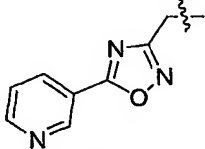
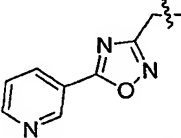
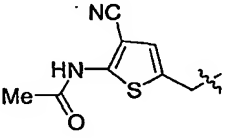
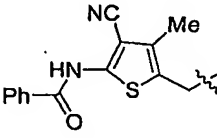
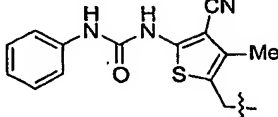
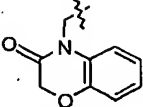
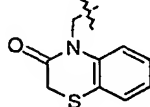
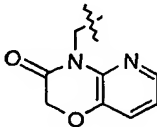
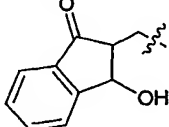
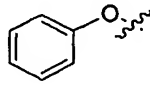
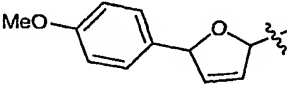
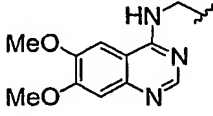
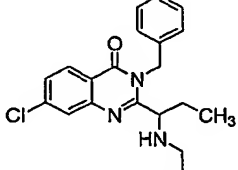
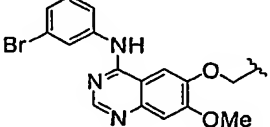
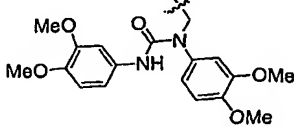
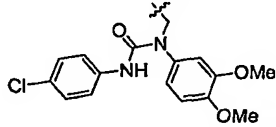
[0097] In a preferred embodiment, the HDAC inhibitors of the invention comprise compounds of paragraph [0058] having formula (3b):



(3b)

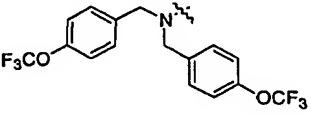
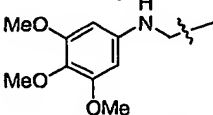
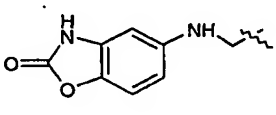
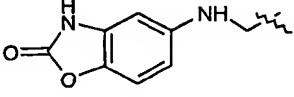
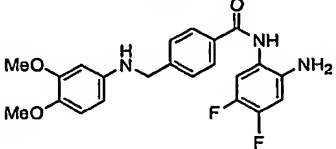
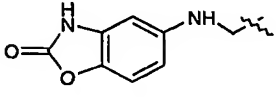
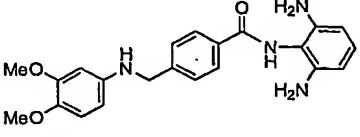
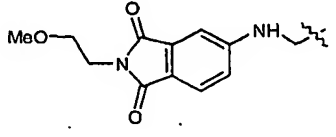
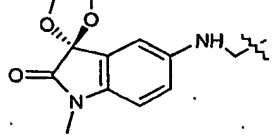
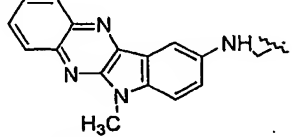
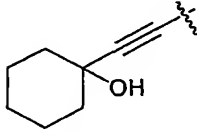
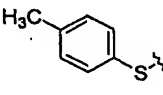
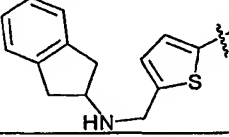
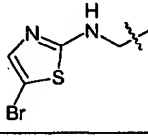
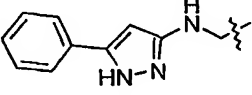
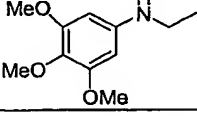
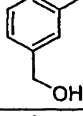
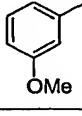
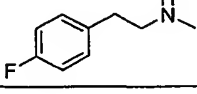

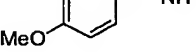
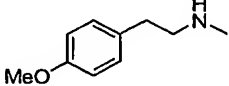
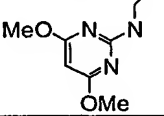
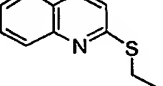
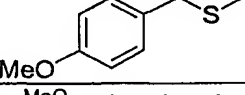
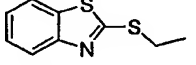
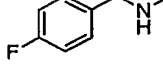
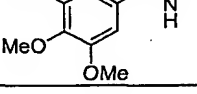
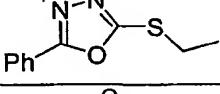
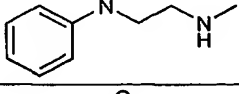
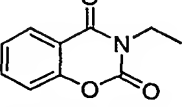
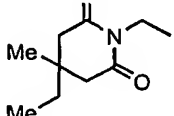
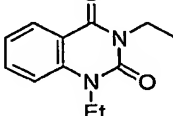
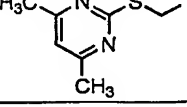
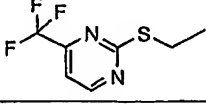
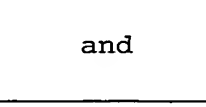
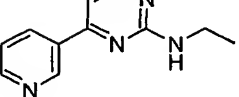
and pharmaceutically acceptable salts thereof, wherein Y and Z are independently N or CH and W is selected from the group consisting of:

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|  | and | |

[0098] In a preferred embodiment of the compounds according to paragraph [0097], the compounds comprise those wherein Y, Z and W are as defined below:

| Cpd | W | Y | Z |
|-----|---|----|----|
| 164 | | CH | CH |
| 165 | | N | CH |
| 166 | | CH | CH |
| 167 | | CH | N |
| 168 | | CH | N |
| 169 | | CH | CH |
| 170 | | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
| 171 | | N | CH |
| 172 | | CH | CH |
| 174 | | CH | N |
| 175 | | CH | N |
| 176 | | CH | N |
| 177 | | CH | CH |
| 178 | | N | CH |
| 179 | | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
| 180 | | CH | CH |
| 181 | | CH | CH |
| 182 | | CH | CH |
| and | | | |
| 183 | | CH | CH |

[0099] In another preferred embodiment of the compounds according to paragraph [0097], the compounds comprise those wherein Y, Z and W are as defined below:

| Cpd | W | Y | Z |
|-----|---|----|----|
| 187 | | CH | CH |
| 188 | | CH | CH |
| 189 | | CH | CH |
| 190 | | CH | CH |
| 193 | | CH | CH |
| 194 | | CH | CH |

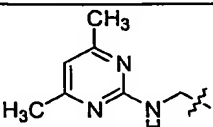
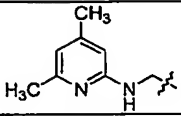
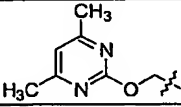
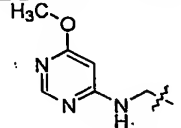
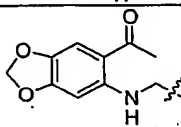
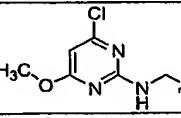
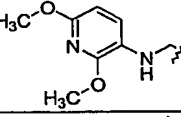
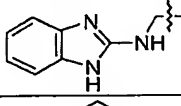
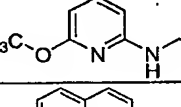
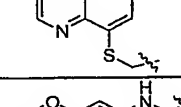
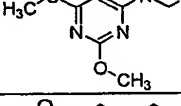
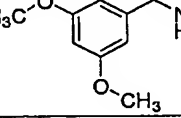
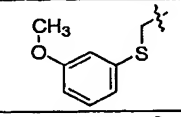
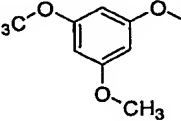
| Cpd | W | Y | Z |
|-----|---|----|----|
| 195 | | CH | CH |
| 196 | | CH | CH |
| 320 | | CH | CH |
| 321 | | CH | CH |
| 322 | | CH | CH |
| 323 | | CH | CH |

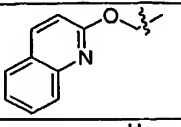
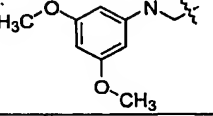
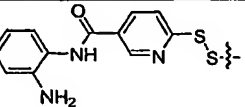
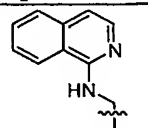
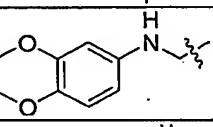
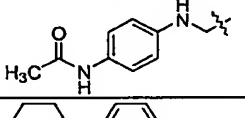
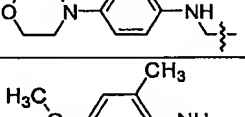
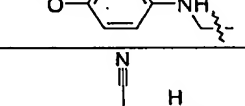
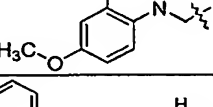
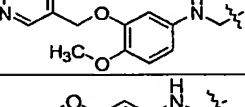
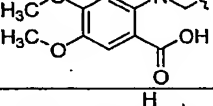
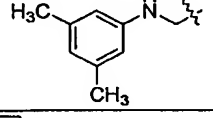
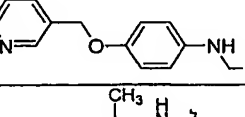
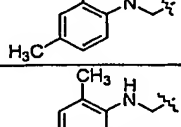
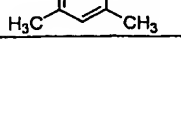
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| 329 | | CH | CH |
| 330 | | CH | CH |
| 331 | | CH | CH |
| 332 | | CH | CH |
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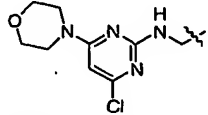
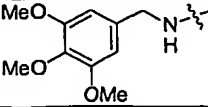
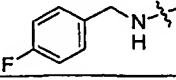
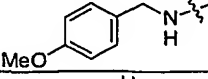
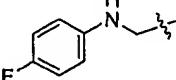
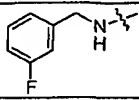
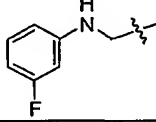
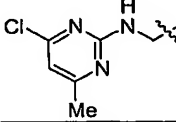
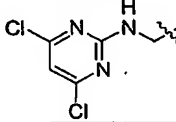
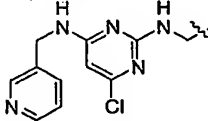
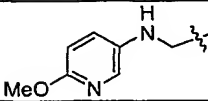
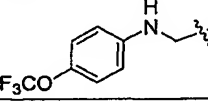
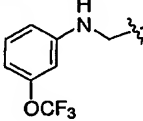
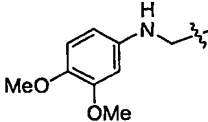
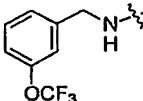
| Cpd | W | Y | Z |
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| 346 | | CH | CH |
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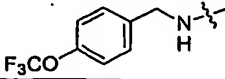
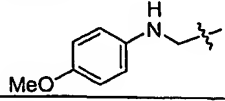
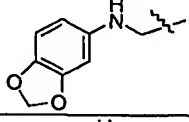
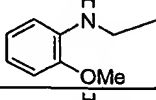
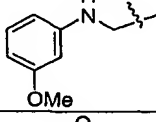
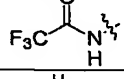
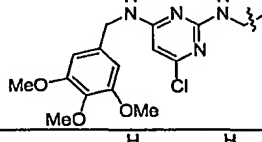
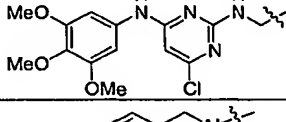
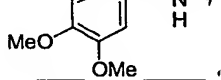
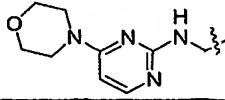
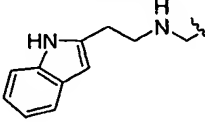
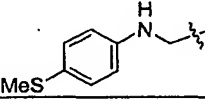
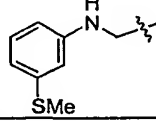
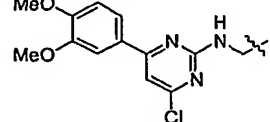
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| 357 | | CH | CH |
| 358 | | CH | CH |
| 359 | | CH | CH |
| 360 | | CH | CH |
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| 362 | | CH | CH |
| 363 | | CH | CH |
| 364 | | CH | CH |
| 365 | | CH | CH |
| 366 | | CH | CH |
| 367 | | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
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| 369 | | CH | CH |
| 370 | | CH | CH |
| 371 | | CH | CH |
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| 373 | | CH | CH |
| 374 | | CH | CH |
| 375 | | CH | CH |
| 377 | | CH | CH |
| 378 | | CH | CH |
| 379 | | CH | CH |
| 380 | | N | CH |
| 381 | | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
| 382 |  | CH | CH |
| 383 |  | CH | CH |
| 384 |  | CH | CH |
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| 387 |  | CH | CH |
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| 390 |  | CH | CH |
| 391 |  | CH | CH |
| 392 |  | CH | CH |
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| 395 |  | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
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| 397 |  | CH | CH |
| 398 |  | CH | N |
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| 410 |  | CH | CH |

| Cpd | W | Y | Z |
|------|---|----|----|
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| 424b |  | CH | CH |
| 425 |  | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
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| 435 |  | CH | CH |
| 436 |  | CH | CH |
| 437 |  | CH | CH |
| 438 |  | CH | CH |
| 439 |  | CH | CH |

| Cpd | W | Y | Z |
|-----|---|----|----|
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| 441 | | CH | CH |
| 442 | | CH | CH |
| 443 | | CH | CH |
| 444 | | CH | CH |
| 445 | | CH | N |
| 446 | | CH | N |
| 447 | | CH | CH |
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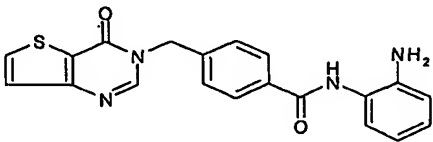
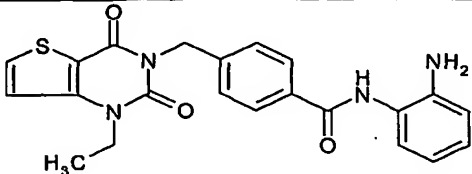
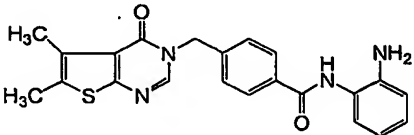
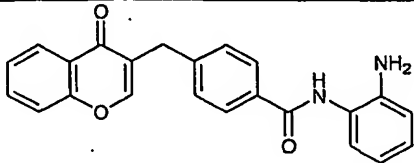
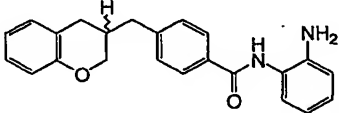
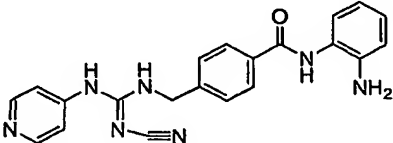
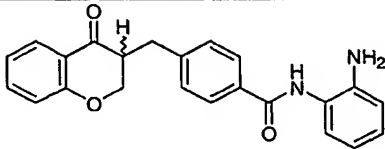
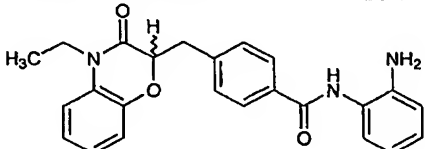
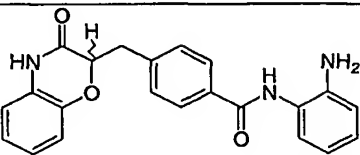
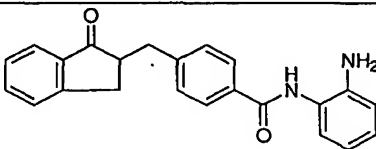
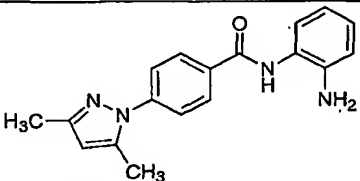
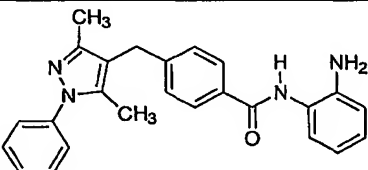
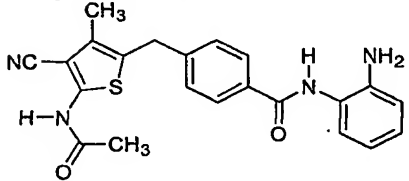
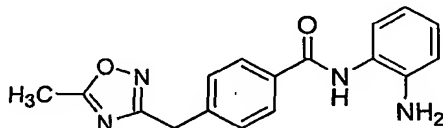
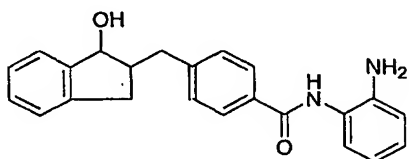
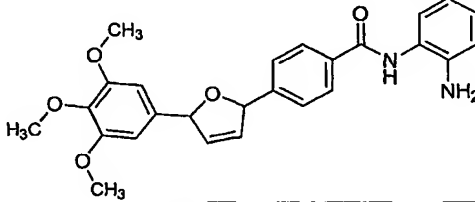
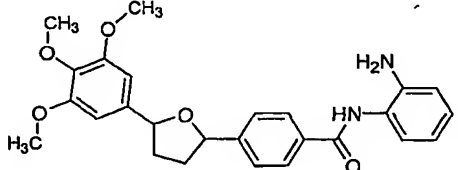
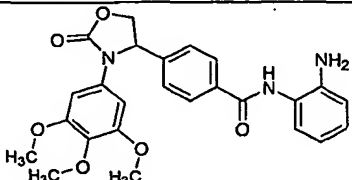
| Cpd | W | Y | Z |
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| 460 | | CH | N |
| 461 | | CH | CH |
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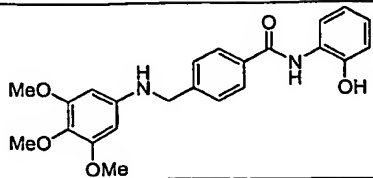
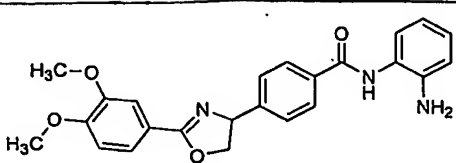
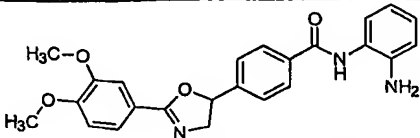
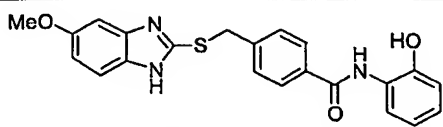
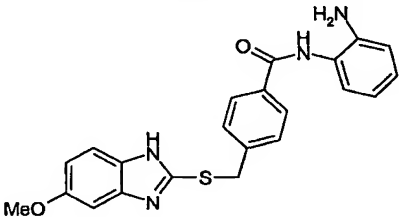
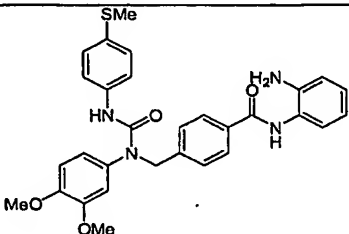
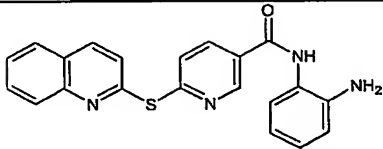
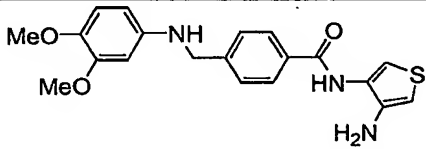
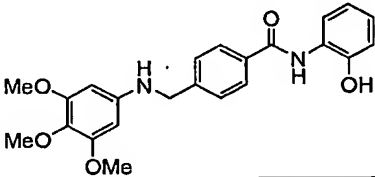
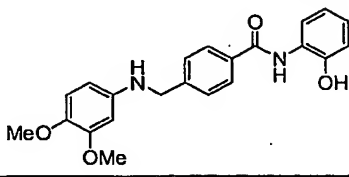
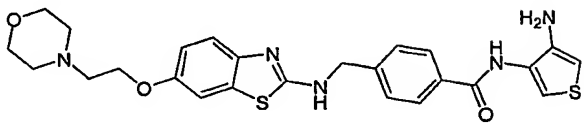
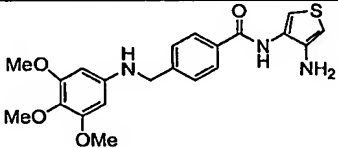
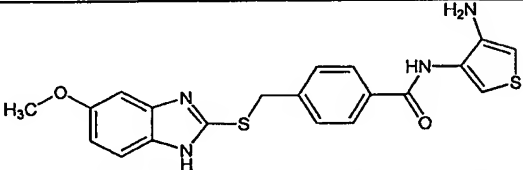
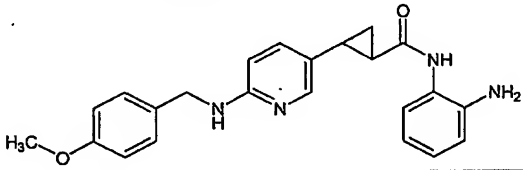
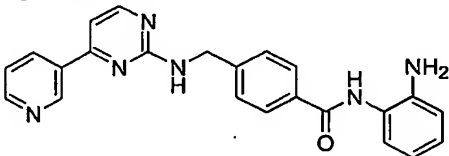
| Cpd | W | Y | Z |
|-----|---|----|----|
| 468 | | CH | CH |

| Cpa | W | Y | Z |
|-----|---|----|----|
| 700 | | CH | CH |

[0100] In yet another preferred embodiment, the novel histone deacetylase inhibitors of the invention are selected from the group consisting of the following and their pharmaceutically acceptable salts:

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[0101] In another preferred embodiment, the compounds are selected from those listed in Tables 2a-b, 3a-d, 4a-c, and 5a-5f.

Synthesis

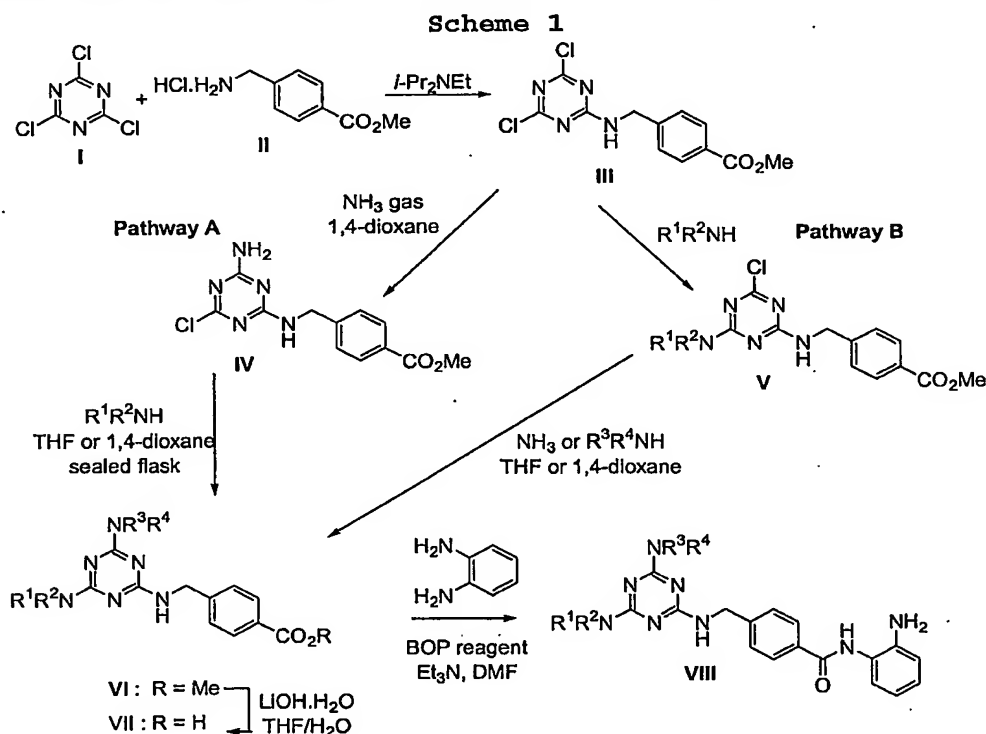
[0102] Compounds of formula (1), wherein Y^1 is $-N(R^1)(R^2)$, preferably may be prepared according to the synthetic route depicted in Scheme 1. Thus, trichlorotriazine I reacts with amine II in the presence of diisopropylethylamine to produce dichloroaminotriazine III. The amine R^1R^2NH is added to dichloroaminotriazine III to produce

diaminochlorotriazine V. Treatment of V with ammonia or R^3R^4NH in tetrahydrofuran (THF) or 1,4 dioxane affords triaminotriazine VI.

[0103] Alternatively, dichloroaminotriazine III may be reacted with ammonia gas in 1,4 dioxane to produce diaminochlorotriazine IV.

Treatment of IV with R^1R^2NH in THF or 1,4 dioxane in a sealed flask then affords triaminotriazine VI.

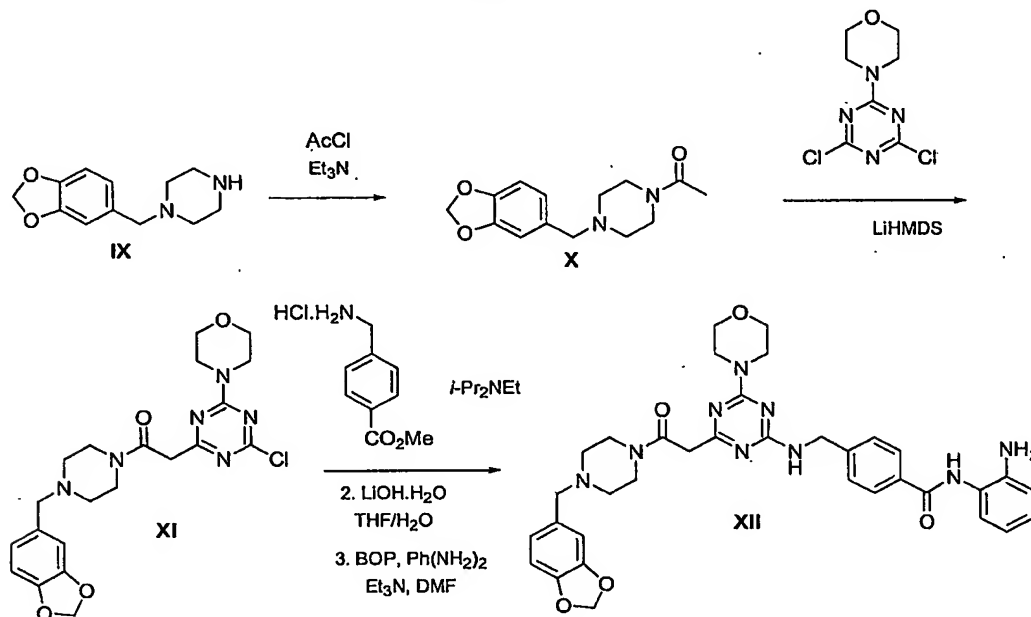
[0104] Hydrolysis of the ester moiety in VI is effected by treatment with a hydroxide base, such as lithium hydroxide, to afford the corresponding acid VII. Treatment of the acid VII with 1,2-phenylenediamine in the presence of BOP reagent, triethylamine, and dimethylformamide (DMF) yields the anilinyll amide VIII.



[0105] Compounds of formula (1), wherein Y^1 is $-CH_2-C(O)-N(R^1)(R^2)$, preferably may be prepared as outlined in Scheme 2. Thus, piperazine

IX is treated with acetyl chloride and triethylamine to produce amide X. Reaction of X with dichloromorpholyltriazine and lithium hexamethyldisiloxane affords compound XI. The chloride of XI is converted to the anilinyll amide of XII as described above with respect to Scheme 1: treatment with the amine and diisopropylethylamine; followed by lithium hydroxide; followed by BOP reagent, phenylenediamine, triethylamine, and DMF.

Scheme 2

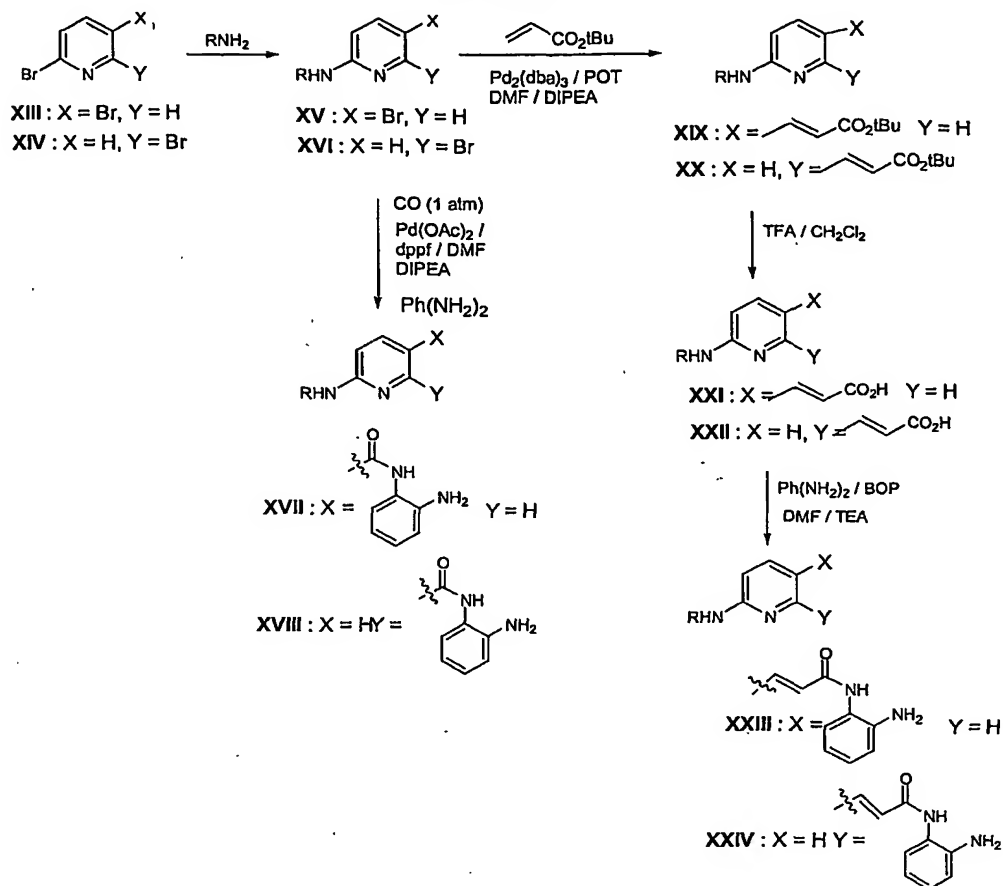


[0106] Compounds of formula (2), wherein Ar^2 is pyridylene and X^1 comprises $-\text{N}(\text{R}^7)-$, compounds of formula (3), wherein Ar^3 is pyridylene and X^2 comprises $-\text{N}(\text{R}^9)-$, and compounds of formula (4), wherein Ar^4 is pyridylene and X^3 comprises $-\text{N}(\text{R}^{11})-$, preferably may be prepared according to the procedures illustrated in Scheme 3. Dibromopyridine XIII or XIV is treated with amine RNH_2 to produce aminobromopyridine XV or XVI, respectively. Treatment of XV or XVI with diacetoxypalladium, diphenylphosphinoferrocene, DMF, diisopropylethylamine, and phenylenediamine under carbon monoxide yields anilinyll amide XVII or XVIII, respectively.

[0107] Treatment of XV or XVI with tert-butylacrylate, diisopropylethylamine, dibenzylacetone palladium, and tri-*o*-tolylphosphine (POT) in DMF under nitrogen affords compounds XIX and XX, respectively. The ester moiety of XIX or XX is hydrolyzed to produce the corresponding acid moiety in XXI or XXII, respectively, by reaction with trifluoroacetic acid in dichloromethane. Treatment of

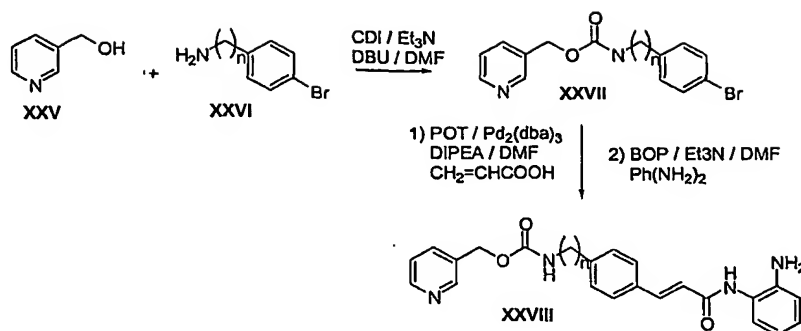
the acid **XXI** or **XXII** with phenylenediamine, BOP, and triethylamine affords the anilinyll amide **XXIII** or **XXIV**, respectively.

Scheme 3



[0108] Compounds of formula (2), wherein X^1 comprises $-O-C(O)-NH-$, preferably may be prepared according to the synthetic route depicted in Scheme 4. Thus, carbinol **XXV** is added to bromobenzylamine **XXVI** with carbonyldiimidazole (CDI), triethylamine, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF to produce compound **XXVII**. The remaining synthetic steps in the production of anilinyll amide **XXVIII** are as described above for Scheme 3.

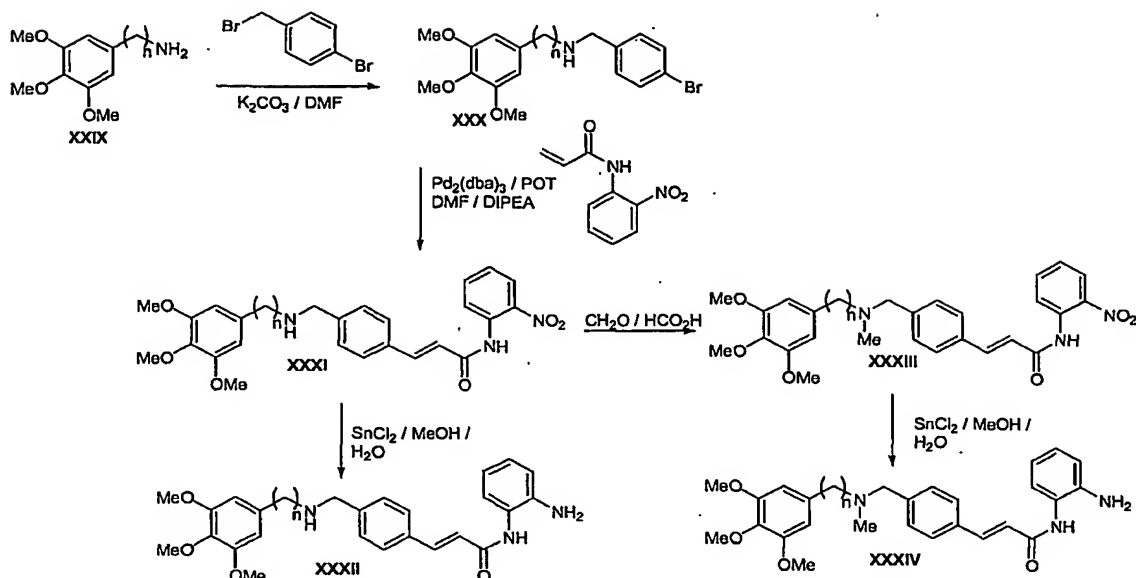
Scheme 4



[0109] Compounds of formula (2), wherein X¹ comprises -N(R⁷)-, preferably may be prepared as outlined in Scheme 5. Amine XXIX is reacted with p-bromobenzylbromide in the presence of potassium carbonate in DMF to produce bromobenzylamine XXX. Treatment of XXX with nitroacrylanilide, dibenzylacetone palladium, POT, and diisopropylethylamine in DMF affords nitroanilide XXXI. Nitroanilide XXXI is converted to the corresponding anilinyll amide XXXII by treatment with stannous chloride in methanol and water.

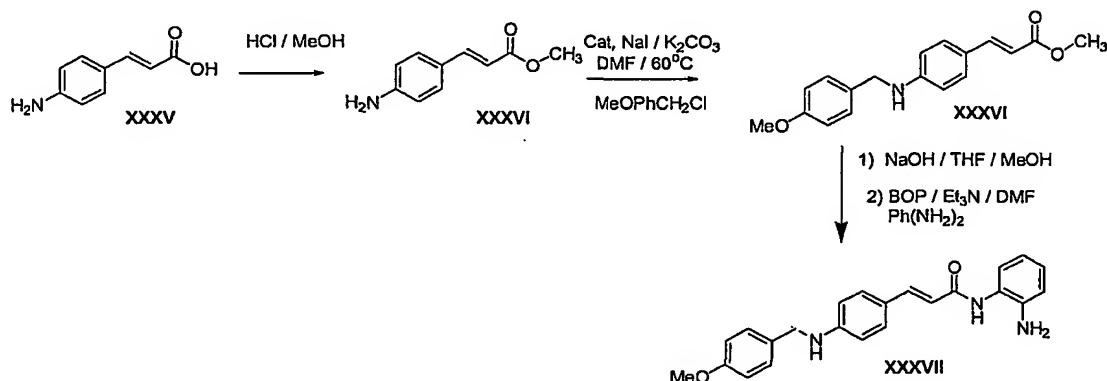
[0110] Treatment of amine XXXI in formic acid with paraformaldehyde provides methylamine XXXIII. The nitroanilide moiety in XXXIII is then converted to the corresponding anilinyll amide moiety in XXXIV by treatment with stannous chloride in methanol and water.


Scheme 5



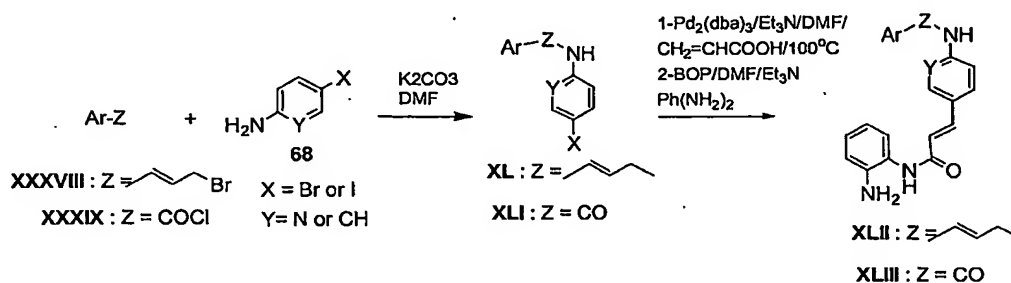
[0111] Alternatively, compounds of formula (2), wherein X^1 comprises $-N(R^7)-$, may be prepared according to the synthetic route depicted in Scheme 6. Carboxylic acid XXXV in methanol is treated with hydrochloric acid to produce ester XXXVI. Conversion of the primary amine moiety in XXXVI to the secondary amine moiety in XXXVI is effected by treatment with a catalyst such as triethylamine, methoxybenzylchloride, sodium iodide, and potassium carbonate in DMF at 60 °C. Ester XXXVI is converted to anilinyln amide XXXVII by treatment with sodium hydroxide, THF, and methanol, followed by BOP, triethylamine, and phenylenediamine in DMF, as described above for Scheme 3.

Scheme 6



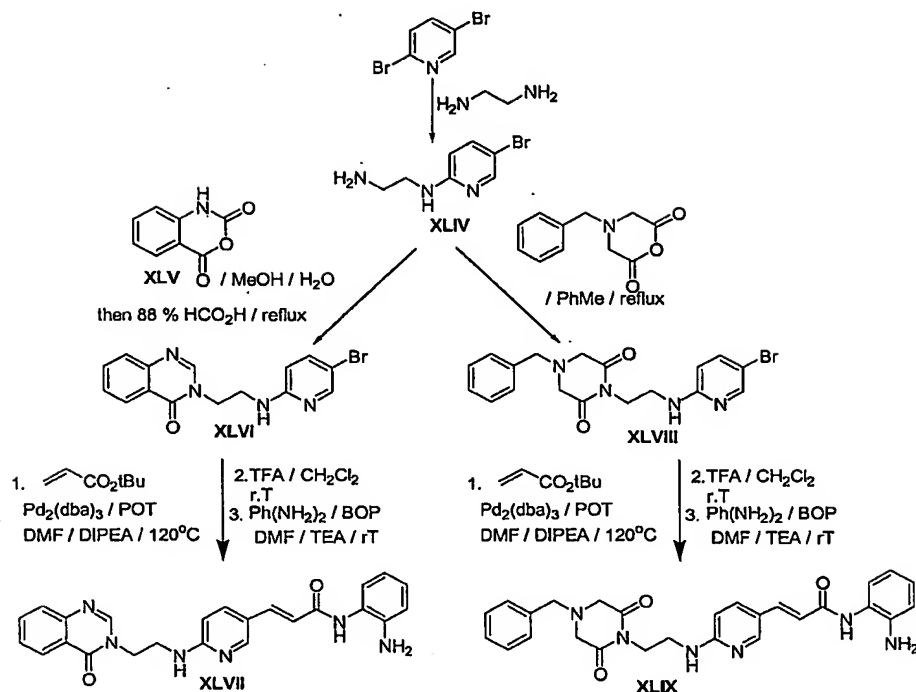
[0112] Compounds of formula (2), wherein X^1 comprises  or $-\text{C}(\text{O})-\text{NH}-$, preferably may be prepared according to the procedures illustrated in Scheme 7. Addition of amine 68 to haloaryl compound XXXVIII or XXXIX and potassium carbonate in DMF provides arylamine XL or XLI, respectively. Anilinyll amide XLII or XLIII is then prepared using procedures analogous to those set forth in Schemes 3-6 above.

Scheme 7



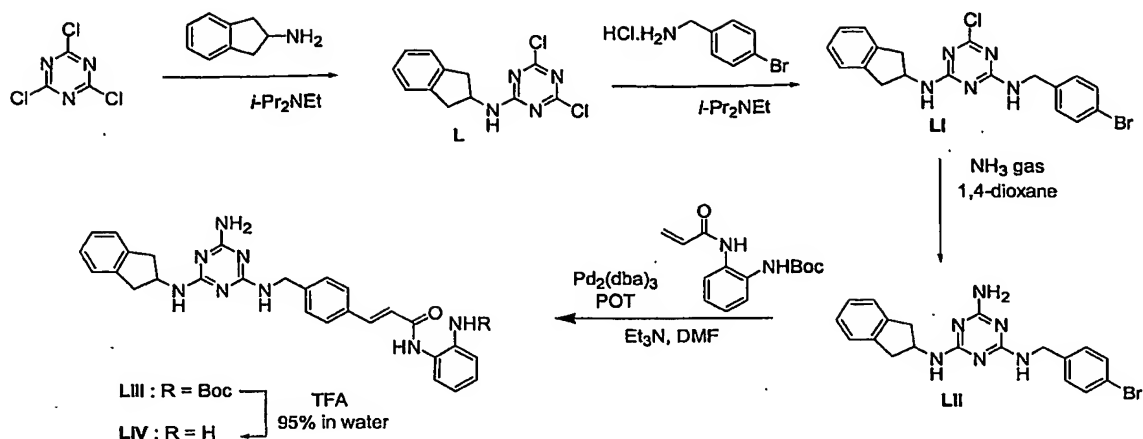
[0113] Compounds such as XLVII and XLIX preferably may be prepared as outlined in Scheme 8. Dibromopyridine is combined with diaminoethane to produce amine XLIV. Treatment of amine XLIV with isatoic anhydride LV in methanol and water, followed by refluxing in formic acid affords compound XLVI. Treatment of amine XLIV with the reaction products of benzylaminodiacetic acid and acetic anhydride provides compound XLVIII. Bromopyridylamines XLVI and XLVIII are then converted to the corresponding diene anilinyll amides XLVII and XLIX, respectively, by procedures analogous to those set forth in Schemes 3-7 above.

Scheme 8



[0114] Compounds such as LIIV preferably may be prepared according to the synthetic route depicted in Scheme 9. Trichlorotriazine is treated with aminoindan and diisopropylethylamine to produce dichloroaminotriazine L. Treatment with bromobenzylamine and diisopropylethylamine affords diaminochlorotriazine LI. Addition of ammonia gas and dioxane provides triaminotriazine LII. Treatment with protected acrylanilide, triethylamine, POT, and dibenzylacetone palladium then yields diene anilinyamide LIII, which is deprotected with trifluoroacetic acid to provide the final product LIIV.

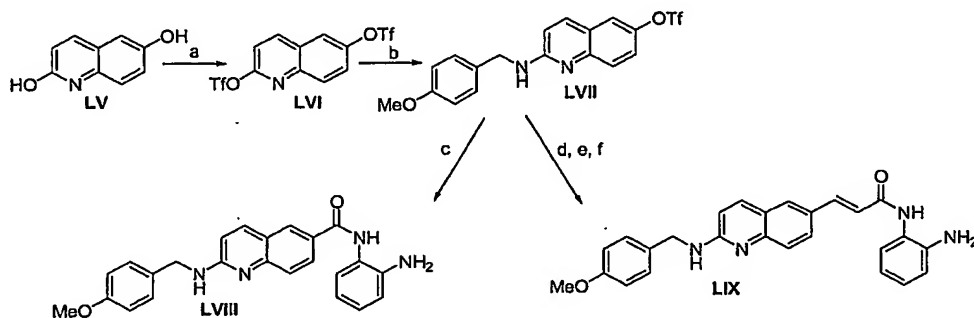
Scheme 9



[0115] Compounds of formula (2), wherein Ar² is quinolylylene and X¹ comprises -N(R⁷)-, compounds of formula (3), wherein Ar³ is quinolylylene and X² comprises -N(R⁹)-, and compounds of formula (4), wherein Ar⁴ is quinolylylene and X³ comprises -N(R¹¹)-, preferably may be prepared according to the procedures illustrated in Scheme 10.

Dihydroxyquinoline LV with dimethylaminopyridine (DMAP) in pyridine is treated with trifluoromethanesulfonyl anhydride to provide bis(trifluoromethanesulfonyloxy)-quinoline LVI. Treatment of LVI with p-methoxybenzylamine affords aminoquinoline LVII. Anilinyll amides LVIII and LIX are then prepared using procedures analogous to those described for Schemes 1-9 above.

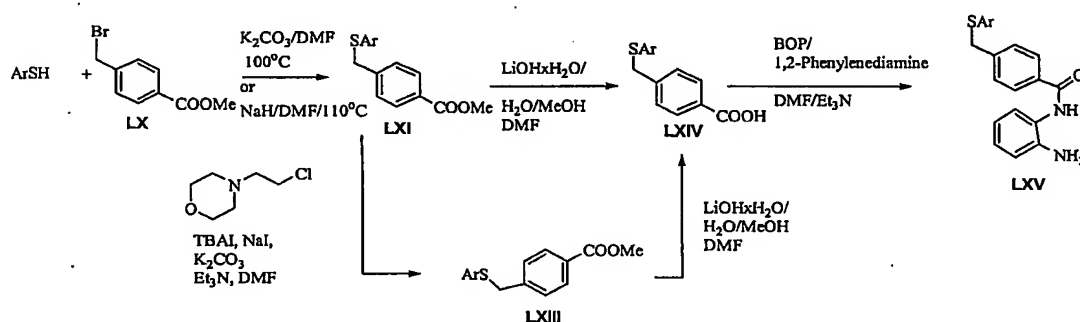
Scheme 10



- a. Tf₂O / Py / DMAP / 0 C
- b. p-methoxybenzylamine / 120 C
- c. 1,2-phenylenediamine / CO (40 ps) / Pd(OAc)₂ / dppf / DMF / DIPEA / 70 C
- d. t Butylacrylate / Pd₂(dba)₃ / POT / DMF / DIPEA / 120 C
- e. TFA / DCM / rT
- f. 1,2-phenylenediamine / BOP / DMF / TEA / rT

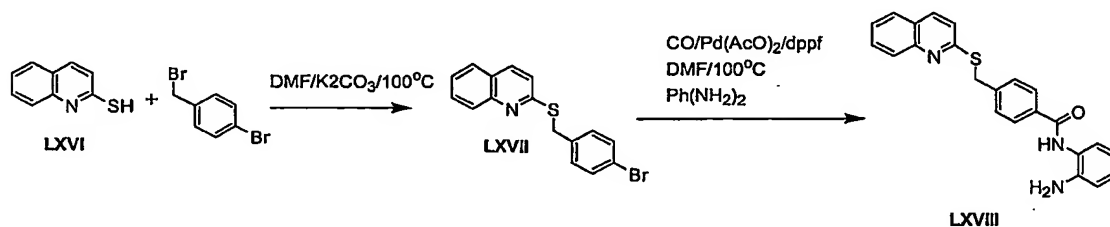
[0116] Compounds of formula (3), wherein X^2 comprises a sulfur atom, and compounds of formula (4), wherein X^3 comprises a sulfur atom, preferably may be prepared as outlined in Scheme 11. Bromide LX is converted to diaryl ester LXI using procedures analogous to those described for Scheme 6 above. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester LXI to the corresponding acid LXIV. Alternatively, ester LXI may be treated with chloroethylmorphonline, sodium iodide, potassium carbonate, triethylamine, and tetrabutylammonium iodide (TBAI) in DMF to produce ester LXIII, which is then converted to acid LXIV as in Scheme 1. Conversion of the acid LXIV to the anilinyll amide LXV is effected by procedures analogous to those set forth in Scheme 1 above.

Scheme 11



[0117] Alternatively, compounds of formula (3), wherein X^2 comprises a sulfur atom, and compounds of formula (4), wherein X^3 comprises a sulfur atom, may be prepared according to the procedures illustrated in Scheme 12. Sulfanyl anilinyllamide LXVIII is prepared using procedures analogous to those set forth in Schemes 3 and 5 above.

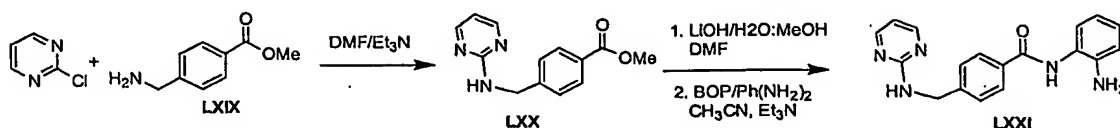
Scheme 12



[0118] Compounds of formula (3), wherein X^2 comprises $-N(R^9)-$, and compounds of formula (4), wherein X^3 comprises $-N(R^{11})-$, preferably may be

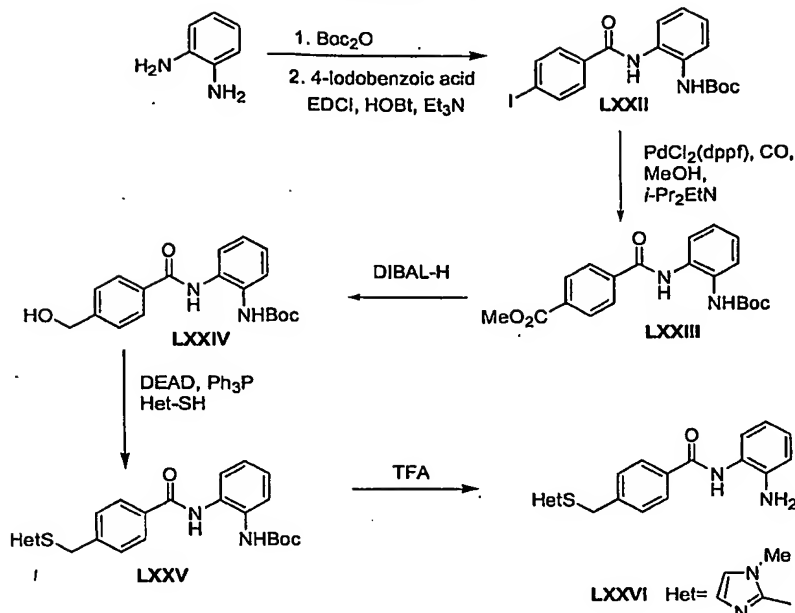
prepared according to the synthetic route depicted in Scheme 13. Amino anilinyll amide LXXI is prepared according to synthetic steps similar to those described for Schemes 1 and 6 above.

Scheme 13



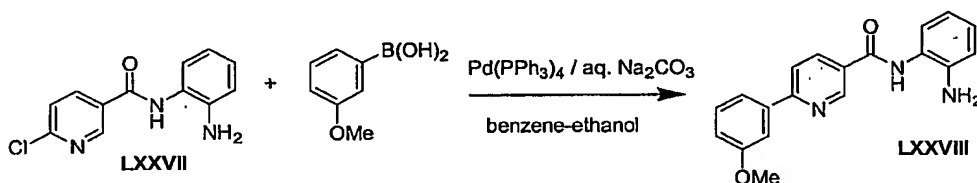
[0119] Compounds of formula (3), wherein X² comprises a sulfur atom, and compounds of formula (4), wherein X³ comprises a sulfur atom, preferably may be prepared as outlined in Scheme 14. Phenylenediamine is reacted with di-tert-butylidicarbonate, followed by iodobenzoic acid, dimethylaminopropylethylcarbodiimide, hydroxybenzotriazole, and triethylamine to provide protected anilinyll amide LXXII. The iodide moiety of LXXII is converted to the methyl ester moiety of LXXIII using procedures analogous to those set forth for Scheme 3 above. The methyl ester moiety of LXXIII is converted to the hydroxyl moiety of LXXIV by treatment with a reducing agent such as diisobutylaluminum hydride (DIBAL-H). Addition of the heterocyclylsulfhydryl compound Het-SH with triphenylphosphine and diethylazodicarboxylate converts the hydroxyl moiety of LXXIV to the sulfanyl moiety of LXXV. LXXV is deprotected with trifluoroacetic acid to afford the sulfanyl anilinyll amide LXXVI.

Scheme 14



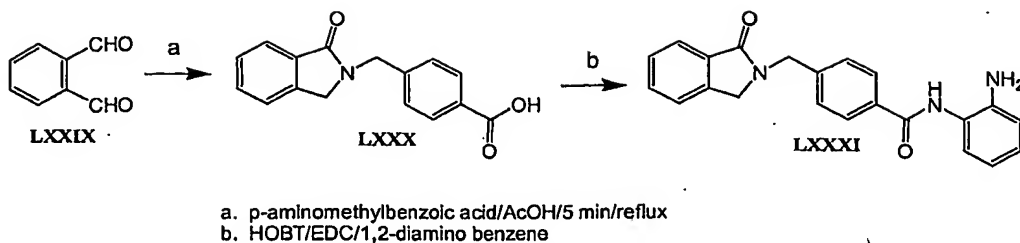
[0120] Compounds of formula (3), wherein X^2 is a chemical bond, preferably may be prepared according to the synthetic route depicted in Scheme 15. Thus, chloroarylanilinyllamide LXXVII is treated with aryl boronic acid, benzene, ethanol, aqueous sodium carbonate, and triphenylphosphine palladium to afford the diarylanilinyllamide LXXVIII.

Scheme 15



[0121] Compounds such as LXXXI preferably may be prepared according to the procedures illustrated in Scheme 16. Thus, benzene-1,2-carbaldehyde LXXIX in acetic acid is treated with p-aminomethylbenzoic acid to produce the benzoic acid LXXX. The acid LXXX is converted to the corresponding anilinyllamide LXXXI by treatment with hydroxybenzotriazole, ethylenedichloride, and phenylenediamine.

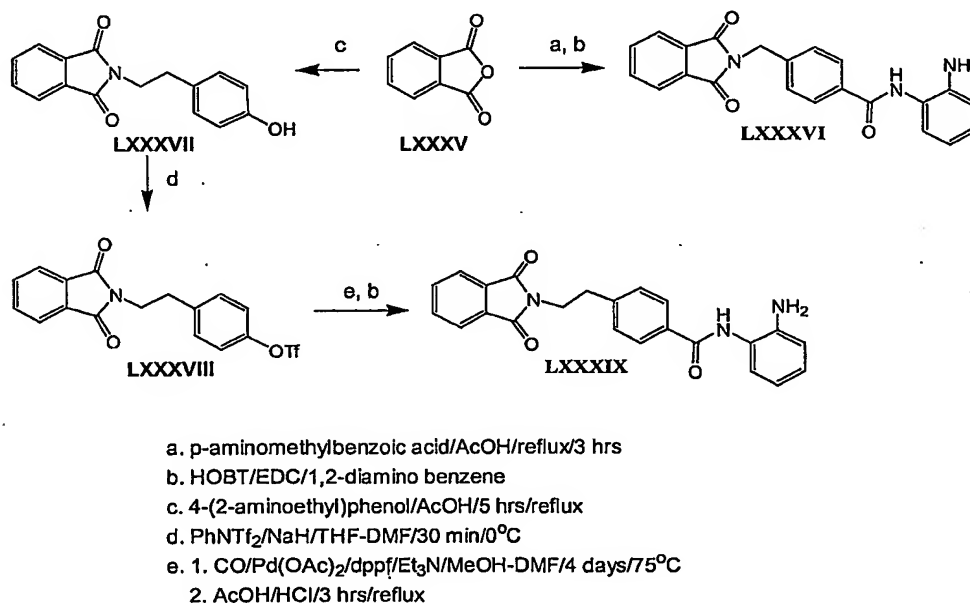
Scheme 16



[0122] Compounds such as LXXXVI and LXXXIX preferably may be prepared according to the procedures illustrated in Scheme 18. Phthalic anhydride LXXXV and p-aminomethylbenzoic acid are combined in acetic acid to produce an intermediate carboxylic acid, which is converted to the anilinyllamide LXXXVI using procedures analogous to those set forth in Schemes 15 and 16 above.

[0123] The addition of 4-(2-aminoethyl)phenol to phthalic anhydride LXXXV in acetic acid affords the hydroxyl compound LXXXVII. The hydroxyl group of LXXXVII is converted to the triflate group of LXXXVIII by treatment with sodium hydride, THF, DMF, and phenylaminoditriplate. Treatment of LXXXVIII according to procedures analogous to those described for Scheme 3 above affords the anilinyllamide LXXXIX.

Scheme 18



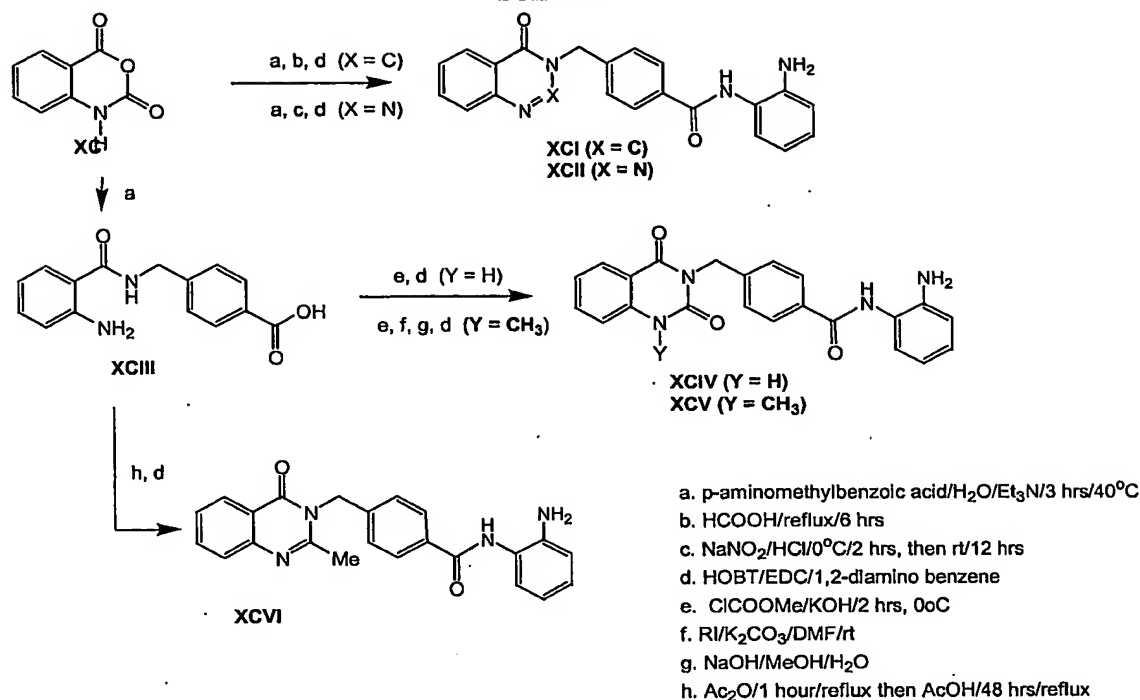
[0124] Compounds such as XCI-XCVI preferably may be prepared according to the synthetic route depicted in Scheme 19. Treatment of isatoic anhydride XC with p-aminomethylbenzoic acid in water and triethylamine, followed by formic acid affords an intermediate carboxylic acid, which is converted to anilinyllamide XCI using procedures analogous to those described for Scheme 16 above.

[0125] Alternatively, treatment of isatoic acid XC with p-aminomethylbenzoic acid in water and triethylamine, followed by hydrochloric acid and sodium nitrite affords an intermediate carboxylic acid, which is converted to anilinyllamide XCII using procedures analogous to those described for Scheme 16 above.

[0126] Alternatively, treatment of isatoic acid XC with p-aminomethylbenzoic acid in water and triethylamine affords benzoic acid XCIII. Treatment of XCIII with sodium hydroxide, dioxane, methylchloroformate, and methanol affords an intermediate quinazolinedione carboxylic acid, the acid moiety of which is then converted to the anilinyllamide moiety of XCIV using procedures analogous to those described for Scheme 16 above. Alternatively, the intermediate quanzolinedione carboxylic acid in DMF is treated with potassium carbonate and methyl iodide to produce an intermediate benzoic acid methyl ester, which is converted to an intermediate benzoic acid by treatment with sodium hydroxide, methanol, and water. The benzoic acid is then converted to the corresponding anilinyllamide XCV using procedures analogous to those described for Scheme 16 above.

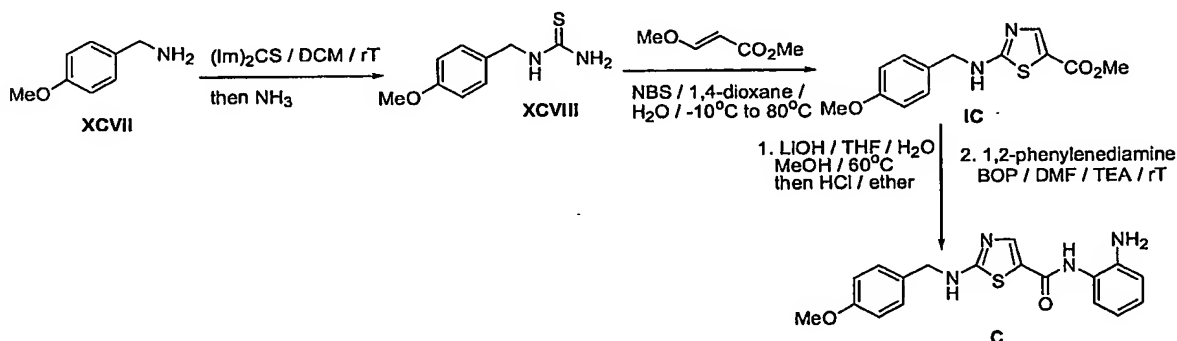
[0127] Alternatively, treatment of XCIII with acetic anhydride followed by acetic acid produces an intermediate carboxylic acid, which is converted to anilinyllamide XCVI using procedures analogous to those described for Scheme 16 above.

Scheme 19



[0128] Compounds such as C preferably may be prepared as outlined in Scheme 20. Alkylamine **XCVII** is treated with thiocarbonyl diimidazole in dichloromethane, followed by ammonium hydroxide to afford thiourea **XCVIII**. Treatment of thiourea **XCVIII** with methylmethoxyacrylate in dioxane and N-bromosuccinimide produces thiazole ester **IC**. The ester **IC** is converted to the corresponding anilinyllamine **C** using procedures analogous to those set forth in Scheme 1 above.

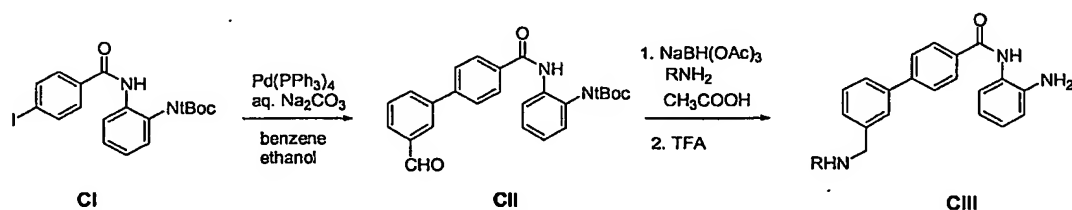
Scheme 20



[0129] Compounds of formula (3), wherein X² is a chemical bond and Cy³ has an amino substituent preferably may be prepared according to the

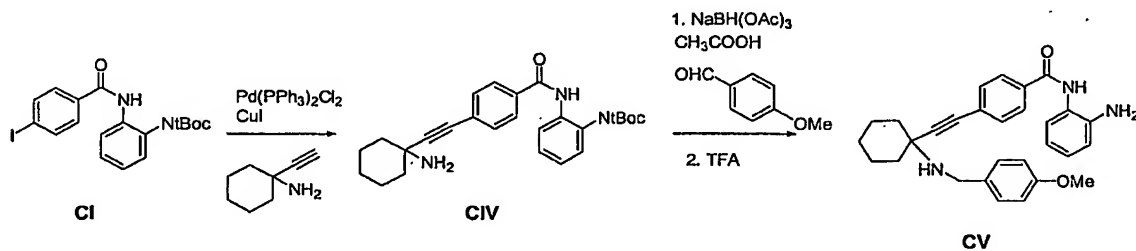
synthetic route depicted in Scheme 21. Thus, protected iodoarylanilinyllamide CI is treated according to procedures analogous to those described for Scheme 15 above afford the diarylanilinyllamide CII. The aldehyde moiety in CII is converted to the corresponding secondary amine moiety by treatment with the primary amine and sodium triacetoxyborohydride followed by glacial acetic acid. The resultant compound is deprotected to yield CIII using procedures analogous to those set forth in Scheme 3 above.

Scheme 21

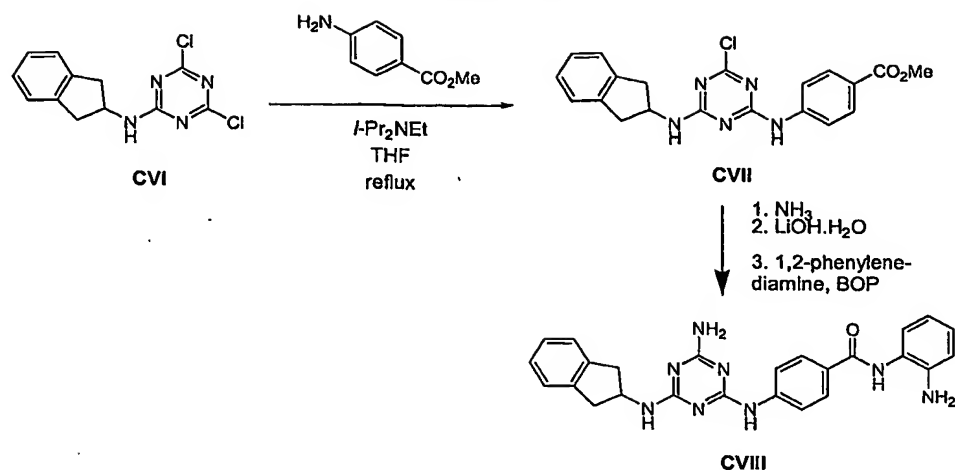


[0130] Compounds of formula (3), wherein X^2 comprises an alkynylene moiety, and compounds of formula (4), wherein X^3 comprises an alkynylene moiety, preferably may be prepared as outlined in Scheme 22. Treatment of protected iodoarylanilinyllamide CI with triphenylphosphine palladium chloride, cuprous iodide, and 1-ethynylcyclohexylamine affords the alkynylarylanilinyllamide CIV. The primary amine moiety in CIV is converted to the corresponding secondary amine and the aniline moiety is deprotected to afford CV using procedures analogous to those described for Scheme 21 above.

Scheme 22

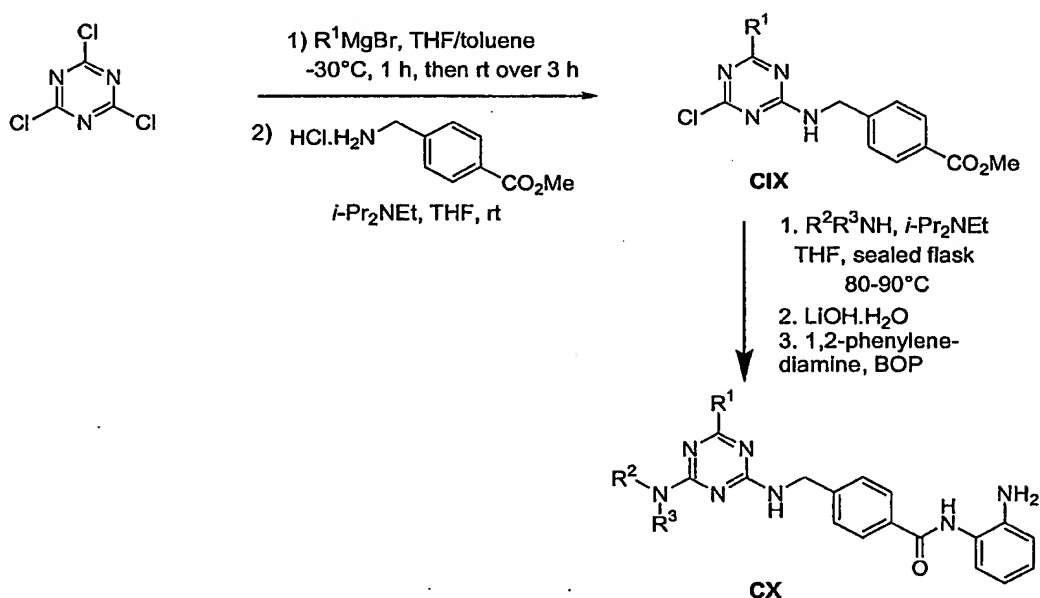


Scheme 24



[0131] Compounds such as CVIII preferably may be prepared according to the synthetic route depicted in Scheme 24. Dichloroaminotriazine CVI is treated with methyl-4-aminobenzoate in the presence of diisopropylethylamine to produce diaminotriazine CVII. Addition of ammonia gas and dioxane, followed by a saponification and a peptide coupling using the same procedures analogous to those described for Scheme 1 above.

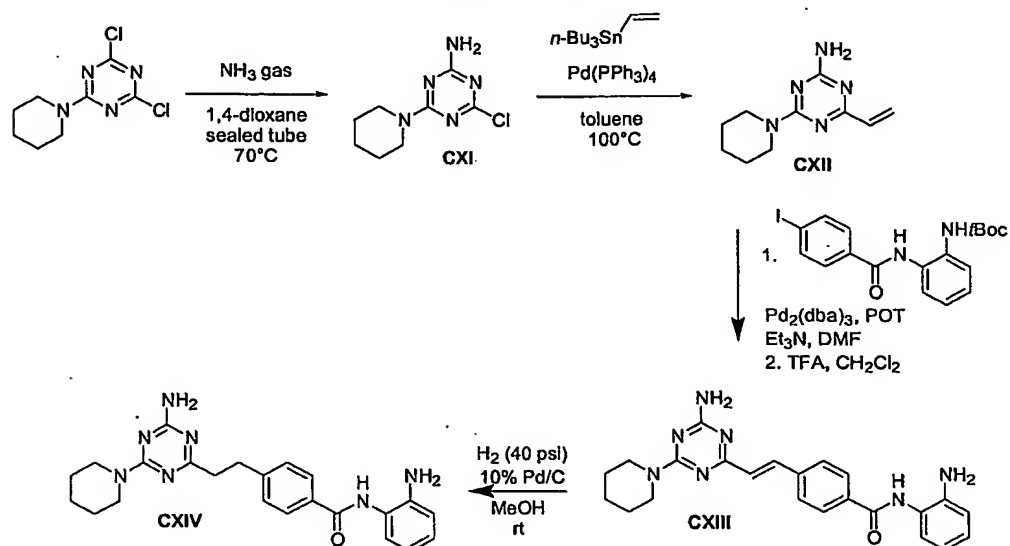
Scheme 30



[0132] Compounds such as CX preferably may be prepared according to the synthetic route depicted in Scheme 30. The Grignard reaction of

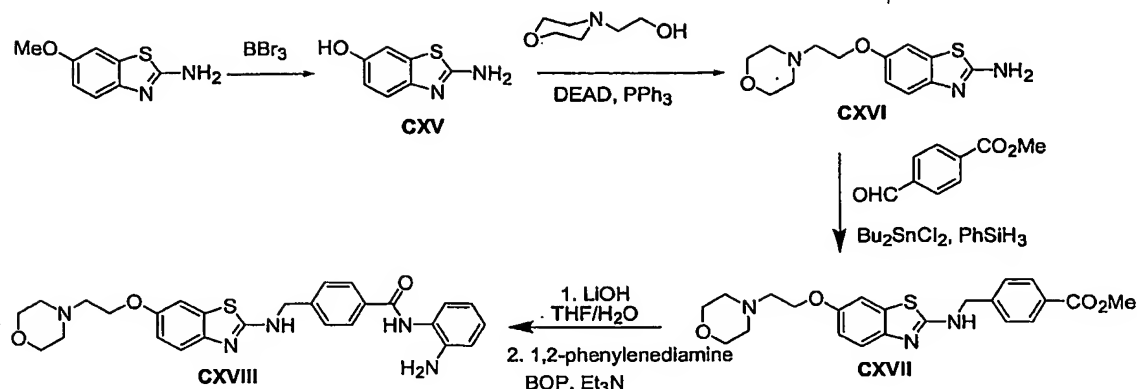
trichloroaminotriazine with various alkyl magnesium bromide, followed by a treatment with methyl-4-aminobenzoate in the presence of diisopropylethylamine yields alkylaminotriazine **CIX**. Synthetic methods similar to those set forth in Scheme 1 above are then used to convert ester **CIX** to the corresponding anilinyll amide **CX**.

Scheme 32



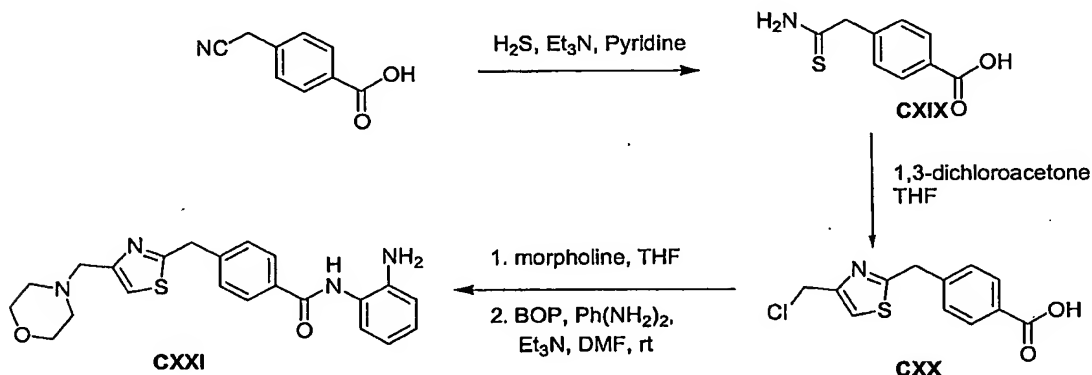
[0133] Amination of dichlorotriazine proceeded using the usual condition described in Scheme 1 to afford **CXI**. Stille coupling using vinyl stannane provides **CXII**. Treatment with protected iodoanilide, triethylamine, POT and dibenzylacetone palladium then yields anilinyllamide, which is deprotected with trifluoroacetic acid to provide the alkene **CXIII**. Hydrogenation of the alkene affords the final compound **CXIV**.

Scheme 33



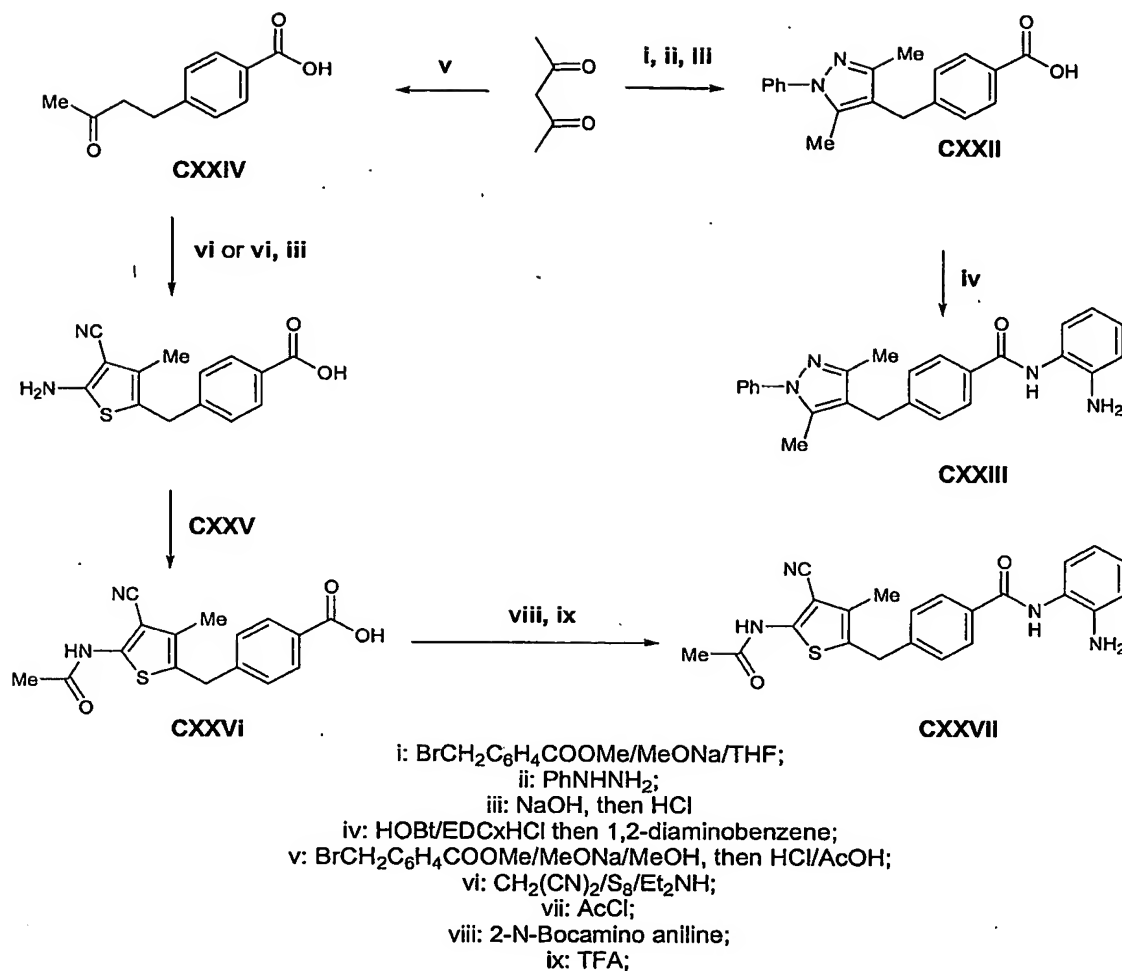
[0134] Compounds such as CXVIII preferably may be prepared according to the synthetic route depicted in Scheme 33. Treatment of methoxyaminobenzothiazole with tribromide boron affords the corresponding acid CXV. Mitsunobu reaction using hydroxyethyl morpholine in the presence of diethylazodicarboxylate and triphenylphosphine yields the amine CXVI. Reductive amination with methyl-4-formylbenzoate using phenylsilane and tin catalyst yields to the ester CXVII. Saponification followed by the usual peptide coupling analogous to those describe for Scheme 1 above provides the desired anilide CXVIII.

Scheme 42



[0135] Treatment 4-methylcyanobenzoic acid with hydrogen sulfide affords CXIX, which is subjected to cyclization in the presence of 1,3-dichloroacetone to yield CXX. Treatment with morpholine followed by a peptide coupling using the standard condition produces CXXI.

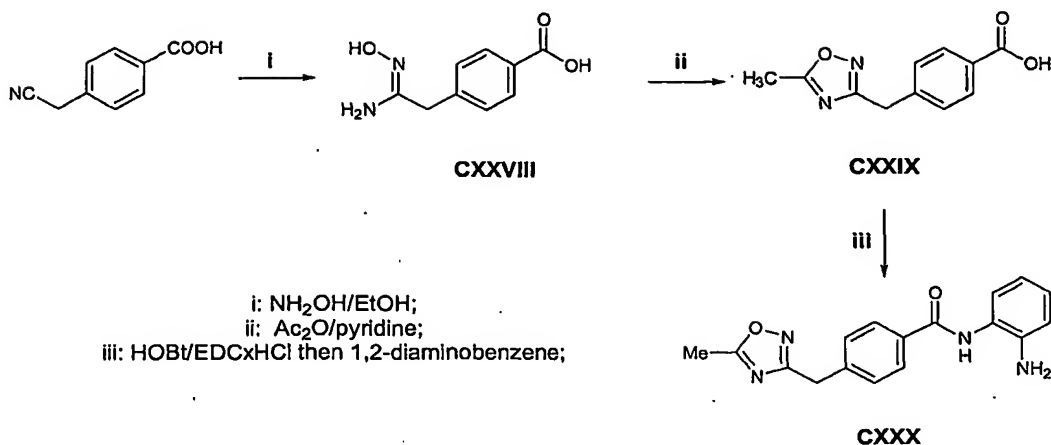
Scheme 49



[0136] Compounds such as CXXIII and CXXVII preferably may be prepared according to the synthetic scheme 49. Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and phenyl hydrazine followed by saponification, afforded the intermediate acid CXXII. This material was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXIII.

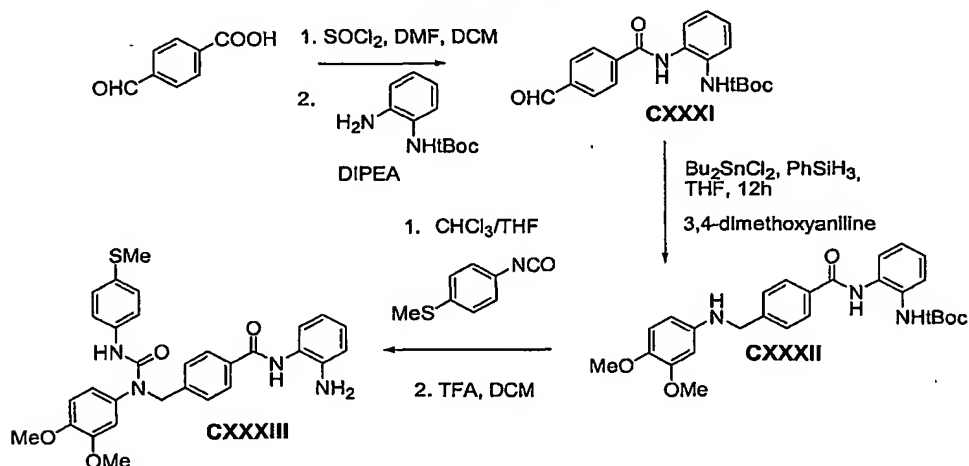
[0137] Consecutive treatment of acetyl acetone with methyl bromomethylbenzoate in the presence of NaOMe and a 1:1 mixture AcOH-HCl (conc.) afforded the intermediate acid CXXIV. This keto-acid reacting with sulfur and malonodinitrile in the presence of a base, produced the thiophene CXXV, which was converted into the desired CXXVII using standard procedures.

Scheme 50



[0138] Compounds such as CXXX preferably may be prepared according to the synthetic scheme 50. Treatment of 4-cyanomethylbenzoic acid with hydroxylamine produced the amidoxime CXXVIII, which upon treatment with acetic anhydride was converted into the oxadiazole CXXIX. The latter was coupled with 1,2-diaminobenzene in a standard fashion to afford CXXX.

Scheme 57



[0139] Compounds such as CXXXIII preferably may be prepared according to the synthetic route depicted in Scheme 57. Treatment of 4-formylbenzoic acid with thionyl chloride afford the acyl chloride which is coupled with protected anilide to produce CXXXI. Reductive amination with dimethoxyaniline using phenylsilane and tin catalyst yields to the protected anilide CXXXII. Treatment with isocyanate followed by

deprotection with trifluoroacetic acid provides the ureidoanilide CXXXIII.

Pharmaceutical Compositions

[0140] In a second aspect, the invention provides pharmaceutical compositions comprising an inhibitor of histone deacetylase according to the invention and a pharmaceutically acceptable carrier, excipient, or diluent. Compounds of the invention may be formulated by any method well known in the art and may be prepared for administration by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0141] The characteristics of the carrier will depend on the route of administration. As used herein, the term "pharmaceutically acceptable" means a non-toxic material that is compatible with a biological system such as a cell, cell culture, tissue, or organism, and that does not interfere with the effectiveness of the biological activity of the active ingredient(s). Thus, compositions according to the invention may contain, in addition to the inhibitor, diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The preparation of pharmaceutically acceptable formulations is described in, e.g., Remington's Pharmaceutical Sciences, 18th Edition, ed. A. Gennaro, Mack Publishing Co., Easton, PA, 1990.

[0142] As used herein, the term pharmaceutically acceptable salts refers to salts that retain the desired biological activity of the above-identified compounds and exhibit minimal or no undesired toxicological effects. Examples of such salts include, but are not limited to acid addition salts formed with inorganic acids (for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalenesulfonic acid, naphthalenedisulfonic acid,

and polygalacturonic acid. The compounds can also be administered as pharmaceutically acceptable quaternary salts known by those skilled in the art, which specifically include the quaternary ammonium salt of the formula $-NR^+ Z^-$, wherein R is hydrogen, alkyl, or benzyl, and Z is a counterion, including chloride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, citrate, tartrate, ascorbate, benzoate, cinnamate, mandelate, benzyloate, and diphenylacetate).

[0143] The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the above-mentioned conditions is in the range from about 0.01 to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient per day. A typical topical dosage will range from 0.01-3% wt/wt in a suitable carrier. The effective dosage range of the pharmaceutically acceptable derivatives can be calculated based on the weight of the parent compound to be delivered. If the derivative exhibits activity in itself, the effective dosage can be estimated as above using the weight of the derivative, or by other means known to those skilled in the art.

Inhibition of Histone Deacetylase

[0144] In a third aspect, the invention provides a method of inhibiting histone deacetylase in a cell, comprising contacting a cell in which inhibition of histone deacetylase is desired with an inhibitor of histone deacetylase according to the invention. Because compounds of the invention inhibit histone deacetylase, they are useful research tools for *in vitro* study of the role of histone deacetylase in biological processes. In addition, the compounds of the invention selectively inhibit certain isoforms of HDAC.

[0145] Measurement of the enzymatic activity of a histone deacetylase can be achieved using known methodologies. For example, Yoshida et al., J. Biol. Chem., 265: 17174-17179 (1990), describes the assessment of histone deacetylase enzymatic activity by the detection of acetylated

histones in trichostatin A treated cells. Taunton et al., Science, 272: 408-411 (1996), similarly describes methods to measure histone deacetylase enzymatic activity using endogenous and recombinant HDAC-1.

[0146] In some preferred embodiments, the histone deacetylase inhibitor interacts with and reduces the activity of all histone deacetylases in the cell. In some other preferred embodiments according to this aspect of the invention, the histone deacetylase inhibitor interacts with and reduces the activity of fewer than all histone deacetylases in the cell. In certain preferred embodiments, the inhibitor interacts with and reduces the activity of one histone deacetylase (e.g., HDAC-1), but does not interact with or reduce the activities of other histone deacetylases (e.g., HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, and HDAC-8). As discussed below, certain particularly preferred histone deacetylase inhibitors are those that interact with, and reduce the enzymatic activity of, a histone deacetylase that is involved in tumorigenesis. Certain other preferred histone deacetylase inhibitors interact with and reduce the enzymatic activity of a fungal histone deacetylase.

[0147] Preferably, the method according to the third aspect of the invention causes an inhibition of cell proliferation of the contacted cells. The phrase "inhibiting cell proliferation" is used to denote an ability of an inhibitor of histone deacetylase to retard the growth of cells contacted with the inhibitor as compared to cells not contacted. An assessment of cell proliferation can be made by counting contacted and non-contacted cells using a Coulter Cell Counter (Coulter, Miami, FL) or a hemacytometer. Where the cells are in a solid growth (e.g., a solid tumor or organ), such an assessment of cell proliferation can be made by measuring the growth with calipers and comparing the size of the growth of contacted cells with non-contacted cells.

[0148] Preferably, growth of cells contacted with the inhibitor is retarded by at least 50% as compared to growth of non-contacted cells. More preferably, cell proliferation is inhibited by 100% (i.e., the contacted cells do not increase in number). Most preferably, the phrase "inhibiting cell proliferation" includes a reduction in the number or size of contacted cells, as compared to non-contacted cells. Thus, an inhibitor of histone deacetylase according to the invention that

inhibits cell proliferation in a contacted cell may induce the contacted cell to undergo growth retardation, to undergo growth arrest, to undergo programmed cell death (i.e., to apoptose), or to undergo necrotic cell death.

[0149] The cell proliferation inhibiting ability of the histone deacetylase inhibitors according to the invention allows the synchronization of a population of asynchronously growing cells. For example, the histone deacetylase inhibitors of the invention may be used to arrest a population of non-neoplastic cells grown in vitro in the G1 or G2 phase of the cell cycle. Such synchronization allows, for example, the identification of gene and/or gene products expressed during the G1 or G2 phase of the cell cycle. Such synchronization of cultured cells may also be useful for testing the efficacy of a new transfection protocol, where transfection efficiency varies and is dependent upon the particular cell cycle phase of the cell to be transfected. Use of the histone deacetylase inhibitors of the invention allows the synchronization of a population of cells, thereby aiding detection of enhanced transfection efficiency.

[0150] In some preferred embodiments, the contacted cell is a neoplastic cell. The term "neoplastic cell" is used to denote a cell that shows aberrant cell growth. Preferably, the aberrant cell growth of a neoplastic cell is increased cell growth. A neoplastic cell may be a hyperplastic cell, a cell that shows a lack of contact inhibition of growth in vitro, a benign tumor cell that is incapable of metastasis in vivo, or a cancer cell that is capable of metastasis in vivo and that may recur after attempted removal. The term "tumorigenesis" is used to denote the induction of cell proliferation that leads to the development of a neoplastic growth. In some embodiments, the histone deacetylase inhibitor induces cell differentiation in the contacted cell. Thus, a neoplastic cell, when contacted with an inhibitor of histone deacetylase may be induced to differentiate, resulting in the production of a non-neoplastic daughter cell that is phylogenetically more advanced than the contacted cell.

[0151] In some preferred embodiments, the contacted cell is in an animal. Thus, the invention provides a method for treating a cell

proliferative disease or condition in an animal, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably, the animal is a mammal, more preferably a domesticated mammal. Most preferably, the animal is a human.

[0152] The term "cell proliferative disease or condition" is meant to refer to any condition characterized by aberrant cell growth, preferably abnormally increased cellular proliferation. Examples of such cell proliferative diseases or conditions include, but are not limited to, cancer, restenosis, and psoriasis. In particularly preferred embodiments, the invention provides a method for inhibiting neoplastic cell proliferation in an animal comprising administering to an animal having at least one neoplastic cell present in its body a therapeutically effective amount of a histone deacetylase inhibitor of the invention.

[0153] It is contemplated that some compounds of the invention have inhibitory activity against a histone deacetylase from a protozoal source. Thus, the invention also provides a method for treating or preventing a protozoal disease or infection, comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a protozoal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0154] The present invention further provides a method for treating a fungal disease or infection comprising administering to an animal in need of such treatment a therapeutically effective amount of a histone deacetylase inhibitor of the invention. Preferably the animal is a mammal, more preferably a human. Preferably, the histone deacetylase inhibitor used according to this embodiment of the invention inhibits a fungal histone deacetylase to a greater extent than it inhibits mammalian histone deacetylases, particularly human histone deacetylases.

[0155] The term "therapeutically effective amount" is meant to denote a dosage sufficient to cause inhibition of histone deacetylase activity in the cells of the subject, or a dosage sufficient to inhibit cell proliferation or to induce cell differentiation in the subject. Administration may be by any route, including, without limitation, parenteral, oral, sublingual, transdermal, topical, intranasal, intratracheal, or intrarectal. In certain particularly preferred embodiments, compounds of the invention are administered intravenously in a hospital setting. In certain other preferred embodiments, administration may preferably be by the oral route.

[0156] When administered systemically, the histone deacetylase inhibitor is preferably administered at a sufficient dosage to attain a blood level of the inhibitor from about 0.01 μM to about 100 μM , more preferably from about 0.05 μM to about 50 μM , still more preferably from about 0.1 μM to about 25 μM , and still yet more preferably from about 0.5 μM to about 25 μM . For localized administration, much lower concentrations than this may be effective, and much higher concentrations may be tolerated. One of skill in the art will appreciate that the dosage of histone deacetylase inhibitor necessary to produce a therapeutic effect may vary considerably depending on the tissue, organ, or the particular animal or patient to be treated.

[0157] In certain preferred embodiments of the third aspect of the invention, the method further comprises contacting the cell with an antisense oligonucleotide that inhibits the expression of a histone deacetylase. The combined use of a nucleic acid level inhibitor (e.g., antisense oligonucleotide) and a protein level inhibitor (i.e., inhibitor of histone deacetylase enzyme activity) results in an improved inhibitory effect, thereby reducing the amounts of the inhibitors required to obtain a given inhibitory effect as compared to the amounts necessary when either is used individually. The antisense oligonucleotides according to this aspect of the invention are complementary to regions of RNA or double-stranded DNA that encode HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC7, and/or HDAC-8 (see e.g., GenBank Accession Number U50079 for HDAC-1, GenBank Accession

Number U31814 for HDAC-2, and GenBank Accession Number U75697 for HDAC-3).

[0158] For purposes of the invention, the term "oligonucleotide" includes polymers of two or more deoxyribonucleosides, ribonucleosides, or 2'-substituted ribonucleoside residues, or any combination thereof. Preferably, such oligonucleotides have from about 6 to about 100 nucleoside residues, more preferably from about 8 to about 50 nucleoside residues, and most preferably from about 12 to about 30 nucleoside residues. The nucleoside residues may be coupled to each other by any of the numerous known internucleoside linkages. Such internucleoside linkages include without limitation phosphorothioate, phosphorodithioate, alkylphosphonate, alkylphosphonothioate, phosphotriester, phosphoramidate, siloxane, carbonate, carboxymethylester, acetamidate, carbamate, thioether, bridged phosphoramidate, bridged methylene phosphonate, bridged phosphorothioate and sulfone internucleoside linkages. In certain preferred embodiments, these internucleoside linkages may be phosphodiester, phosphotriester, phosphorothioate, or phosphoramidate linkages, or combinations thereof. The term oligonucleotide also encompasses such polymers having chemically modified bases or sugars and/ or having additional substituents, including without limitation lipophilic groups, intercalating agents, diamines and adamantane.

[0159] For purposes of the invention the term "2'-substituted ribonucleoside" includes ribonucleosides in which the hydroxyl group at the 2' position of the pentose moiety is substituted to produce a 2'-O-substituted ribonucleoside. Preferably, such substitution is with a lower alkyl group containing 1-6 saturated or unsaturated carbon atoms, or with an aryl or allyl group having 2-6 carbon atoms, wherein such alkyl, aryl or allyl group may be unsubstituted or may be substituted, e.g., with halo, hydroxy, trifluoromethyl, cyano, nitro, acyl, acyloxy, alkoxy, carboxyl, carbalkoxyl, or amino groups. The term "2'-substituted ribonucleoside" also includes ribonucleosides in which the 2'-hydroxyl group is replaced with an amino group or with a halo group, preferably fluoro.

[0160] Particularly preferred antisense oligonucleotides utilized in this aspect of the invention include chimeric oligonucleotides and hybrid oligonucleotides.

[0161] For purposes of the invention, a "chimeric oligonucleotide" refers to an oligonucleotide having more than one type of internucleoside linkage. One preferred example of such a chimeric oligonucleotide is a chimeric oligonucleotide comprising a phosphorothioate, phosphodiester or phosphorodithioate region, preferably comprising from about 2 to about 12 nucleotides, and an alkylphosphonate or alkylphosphonothioate region (see e.g., Pederson et al. U.S. Patent Nos. 5,635,377 and 5,366,878). Preferably, such chimeric oligonucleotides contain at least three consecutive internucleoside linkages selected from phosphodiester and phosphorothioate linkages, or combinations thereof.

[0162] For purposes of the invention, a "hybrid oligonucleotide" refers to an oligonucleotide having more than one type of nucleoside. One preferred example of such a hybrid oligonucleotide comprises a ribonucleotide or 2'-substituted ribonucleotide region, preferably comprising from about 2 to about 12 2'-substituted nucleotides, and a deoxyribonucleotide region. Preferably, such a hybrid oligonucleotide contains at least three consecutive deoxyribonucleosides and also contains ribonucleosides, 2'-substituted ribonucleosides, preferably 2'-O-substituted ribonucleosides, or combinations thereof (see e.g., Meteleev and Agrawal, U.S. Patent No. 5,652,355).

[0163] The exact nucleotide sequence and chemical structure of an antisense oligonucleotide utilized in the invention can be varied, so long as the oligonucleotide retains its ability to inhibit expression of the gene of interest. This is readily determined by testing whether the particular antisense oligonucleotide is active. Useful assays for this purpose include quantitating the mRNA encoding a product of the gene, a Western blotting analysis assay for the product of the gene, an activity assay for an enzymatically active gene product, or a soft agar growth assay, or a reporter gene construct assay, or an in vivo tumor growth assay, all of which are described in detail in this specification or in Ramchandani et al. (1997) Proc. Natl. Acad. Sci. USA 94: 684-689.

[0164] Antisense oligonucleotides utilized in the invention may conveniently be synthesized on a suitable solid support using well known chemical approaches, including H-phosphonate chemistry, phosphoramidite chemistry, or a combination of H-phosphonate chemistry and phosphoramidite chemistry (i.e., H-phosphonate chemistry for some cycles and phosphoramidite chemistry for other cycles). Suitable solid supports include any of the standard solid supports used for solid phase oligonucleotide synthesis, such as controlled-pore glass (CPG) (see, e.g., Pon, R.T. (1993) Methods in Molec. Biol. 20: 465-496).

[0165] Particularly preferred oligonucleotides have nucleotide sequences of from about 13 to about 35 nucleotides which include the nucleotide sequences shown in Table 1. Yet additional particularly preferred oligonucleotides have nucleotide sequences of from about 15 to about 26 nucleotides of the nucleotide sequences shown in Table 1.

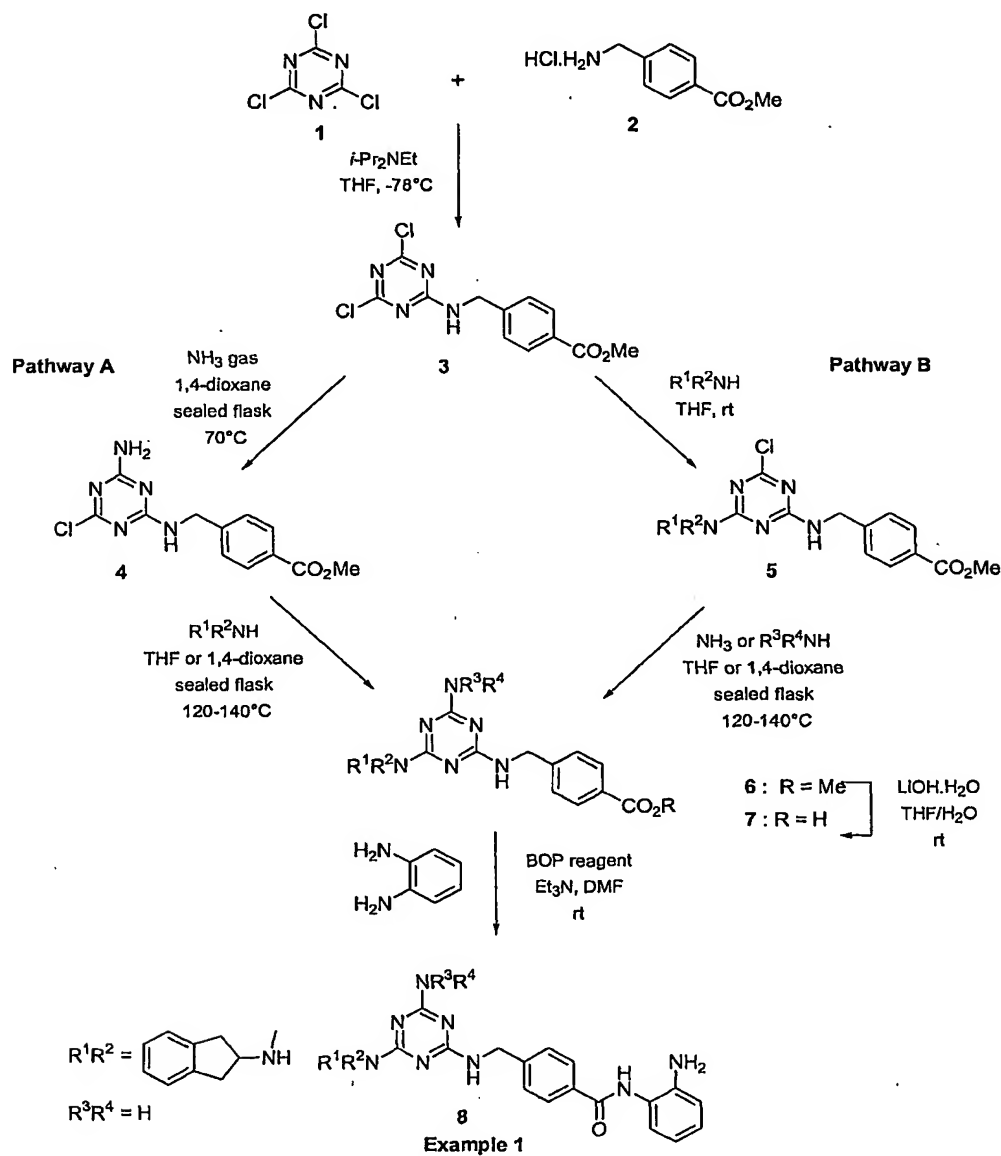
Table 1

| Oligo | Target | Accession Number | Nucleotide Position | Sequence | position within Gene |
|-----------|-------------|------------------|---------------------|-----------------------------|----------------------|
| HDAC1 AS1 | Human HDAC1 | U50079 | 1585-1604 | 5'-GAAACGTGAGGGACTCAGCA-3' | 3'-UTR |
| HDAC1 AS2 | Human HDAC1 | U50079 | 1565-1584 | 5'-GGAAGCCAGAGCTGGAGAGG-3' | 3'-UTR |
| HDAC1 MM | Human HDAC1 | U50079 | 1585-1604 | 5'-GTTAGGTGAGGCACCTGAGGA-3' | 3'-UTR |
| HDAC2 AS | Human HDAC2 | U31814 | 1643-1622 | 5'-GCTGAGCTGTTCTGATTGG-3' | 3'-UTR |
| HDAC2 MM | Human HDAC2 | U31814 | 1643-1622 | 5'-CGTGAGCACTTCTCATTTCC-3' | 3'-UTR |
| HDAC3 AS | Human HDAC3 | AF039703 | 1276-1295 | 5'-CGCTTTCTTGTGTCATTGACA-3' | 3'-UTR |
| HDAC3 MM | Human HDAC3 | AF039703 | 1276-1295 | 5'-GCCTTTCTTACTCATTTGTGT-3' | 3'-UTR |
| HDAC4 AS1 | Human HDAC4 | AB006626 | 514-33 | 5'-GCTGCCTGCCGTGCCCAACCC-3' | 5'-UTR |
| HDAC4 MM1 | Human HDAC4 | AB006626 | 514-33 | 5'-CGTGCCTGCCGTGCCCAACGG-3' | 5'-UTR |
| HDAC4 AS2 | Human HDAC4 | AB006626 | 7710-29 | 5'-TACAGTCCATGCAACCTCCA-3' | 3'-UTR |
| HDAC4 MM4 | Human HDAC4 | AB006626 | 7710-29 | 5'-ATCAGTCCAACCAACCTCGT-3' | 3'-UTR |
| HDAC5 AS | Human HDAC5 | AF039691 | 2663-2682 | 5'-CTTCGGTCTCACCTGCTTGG-3' | 3'-UTR |
| HDAC6 AS | Human HDAC6 | AJ011972 | 3791-3810 | 5'-CAGGCTGGAATGAGCTACAG-3' | 3'-UTR |
| HDAC6 MM | Human HDAC6 | AJ011972 | 3791-3810 | 5'-GACGCTGCAATCAGGTAGAC-3' | 3'-UTR |
| HDAC7 AS | Human HDAC7 | AF239243 | 2896-2915 | 5'-CTTCAGCCAGGATGCCCA-3' | 3'-UTR |

| Oligo | Target | Accession Number | Nucleotide Position | Sequence | position within Gene |
|-----------|-------------|---------------------|------------------------|--------------------------------|----------------------------|
| | | | | 3' | |
| HDAC8 AS1 | Human HDAC8 | AF230097 | 51-70 | 5'-CTCCGGCTCCTCCATCTTCC- 3' | 5'-UTR |
| HDAC8 AS2 | Human HDAC8 | AF230097 | 1328-1347 | 5'-AGCCAGCTGCCACTTGATGC- 3' | 3'-UTR |

[0166] The following examples are intended to further illustrate certain preferred embodiments of the invention, and are not intended to limit the scope of the invention.

EXAMPLES



Example 1

4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (compound 8)

Step 1: Methyl-4-[(4,6-dichloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 3)

[0167] To a stirred solution at -78°C of cyanuric chloride 1 (8.23 g, 44.63 mmol) in anhydrous THF (100 mL) under nitrogen was added a suspension of methyl 4-(aminomethyl)benzoate.HCl 2 (10.00 g, 49.59 mmol), in anhydrous THF (50 mL), followed by $i\text{-Pr}_2\text{NEt}$ (19.00 mL, 109.10 mmol). After 30 min, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ CH_2Cl_2 : 5/95) to afford the title compound 3 (12.12 g, 38.70 mmol, 87% yield) as a pale yellow solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm): AB system (δ_{A} = 8.04, δ_{B} = 7.38, J = 8.5 Hz, 4H), 6.54 (bt, 1H), 4.76 (d, J = 6.3 Hz, 2H), 3.93 (s, 3H).

Pathway A

Step 2: Methyl-4-[(4-amino-6-chloro-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 4)

[0168] In a 150 mL sealed flask, a solution of 3 (6.00 g, 19.16 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH_3 gas for 5 min, and warmed to 70°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH_3 gas was repeated at room temperature for 5 min, and the reaction mixture was warmed to 70°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ CH_2Cl_2 : 30/70) to afford the title compound 4 (5.16 g, 17.57 mmol, 91% yield) as

a white solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm): AB system ($\delta_A = 8.01$, $\delta_B = 7.35$, $J = 8.1$ Hz, 4H), 5.79 (bs, 1H), 5.40-5.20 (m, 2H), 4.72-4.63 (m, 2H), 3.91 (s, 3H).

Pathway B

Step 2: Methyl 4-[(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 5)

[0169] To a stirred solution at room temperature of 3 (3.00 g, 9.58 mmol) in anhydrous THF (50 mL) under nitrogen were added *i*-Pr₂NEt (8.34 mL, 47.90 mmol) and 2-aminoindan.HCl (1.95 g, 11.50 mmol) or R¹R²NH (1.2 equiv), respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated to afford the title compound 5 (4.06 g, 9.91 mmol, quantitative yield) as a white powder. ^1H NMR (300 MHz, CDCl_3) δ (ppm): mixture of rotamers, 8.06-7.94 (m, 2H), 7.43-7.28 (m, 2H), 7.24-7.12 (m, 4H), 6.41 and 6.05 (2 bt, 1H), 5.68-5.44 (m, 1H), 4.92-4.54 (m, 3H), 3.92 (bs, 3H), 3.41-3.12 (m, 2H), 2.90-2.70 (m, 2H).

Step 3: Methyl-4-[(4-amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoate (compound 6)

General procedure for the amination with NH_3 gas:

[0170] In a 150 mL sealed flask, a solution of 5 (3.90 g, 9.51 mmol) in anhydrous 1,4-dioxane (80 mL) was stirred at room temperature, saturated with NH_3 gas for 5 min, and warmed to 140°C for 6 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH_3 gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 18 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$: 3/97) to afford the title compound 6 (3.50 g, 8.96 mmol, 94% yield) as a pale yellow sticky solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.99 (bd, $J = 8.2$ Hz, 2H),

7.41-7.33 (m, 2H), 7.24-7.13 (m, 4H), 5.50-5.00 (m, 2H), 4.90-4.55 (m, 5H), 3.92 (s, 3H), 3.40-3.10 (m, 2H), 2.90-2.70 (m, 2H). ¹³C NMR: (75 MHz, CDCl₃) δ (ppm): 166.88, 167.35, 166.07, 144.77, 141.07, 129.82, 128.93, 127.01, 126.61, 124.70, 52.06, 51.80, 44.25, 40.16. HRMS (calc.): 390.1804, (found): 390.1800.

Pathways A and B, step 3, general procedure with primary and/or secondary amines:

[0171] In a 50-75 mL sealed flask, a stirred solution of 4 (500 mg, 1.70 mmol, 1 equiv), *i*-Pr₂NEt (1.48 mL, 8.51 mmol, 5 equiv) and R¹R²NH or R³R⁴NH (1.5-3 equiv) in anhydrous THF or 1,4-dioxane (20-30 mL) was warmed to 120-140°C for 15-24 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel to afford the title compound.

Step 4: 4-[(4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (compound 7)

[0172] To a stirred solution at room temperature of 6 (2.07 g, 5.30 mmol) in THF (50 mL) was added a solution of LiOH.H₂O (334 mg, 7.96 mmol) in water (25 mL). After 18 h, the reaction mixture was diluted in water and acidified with 1 N HCl until pH 5-6 in order to get a white precipitate. After 1 h, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound 7 (1.73 g, 4.60 mmol, 87% yield) as a white solid. ¹H NMR (300 MHz, acetone-d₆) δ (ppm): 8.05 (bd, J = 8.1 Hz, 2H), 7.56-7.42 (m, 2H), 7.30-7.10 (m, 4H), 5.90-5.65 (m, 2H), 4.85-4.60 (m, 4H), 3.40-2.80 (m, 4H). HRMS (calc.): 376.1648, (found): 376.1651.

Step 5: 4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (compound 8)

[0173] To a stirred solution at room temperature of 7 (200 mg, 0.53 mmol) in anhydrous DMF (5 mL) under nitrogen were added Et₃N (74 μl, 0.53 mmol) and BOP reagent (282 mg, 0.64 mmol), respectively. After 40 min, a solution of 1,2-phenylenediamine (64 mg, 0.58 mmol), Et₃N (222 μl, 1.59

mmol) in anhydrous DMF (2 mL) was added dropwise. After 1.5 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$: 2/98→5/95) to afford the title compound **8** (155 mg, 0.33 mmol, 63% yield) as a pale yellow foam.

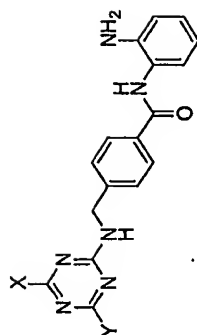
^1H NMR (300 MHz, acetone- d_6) δ (ppm): 9.04 (bs, 1H), 7.96 (bd, $J = 8.0$ Hz, 2H), 7.50-7.40 (m, 2H), 7.30 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H), 7.22-7.08 (m, 4H), 6.99 (ddd, $J = 8.0$ Hz, 7.5 Hz, 1.5 Hz, 1H), 6.86 (dd, $J = 8.0$ Hz, 1.4 Hz, 1H), 6.67 (dt, $J = 7.5$ Hz, 1.4 Hz, 1H), 6.60-5.49 (m, 4H), 4.80-4.50 (m, 4H), 3.30-3.08 (m, 2H), 2.96-2.74 (m, 2H).

EXAMPLES 2-28

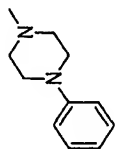
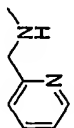
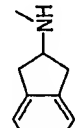
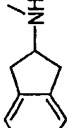
[0174] Examples 2 to 28 describe the preparation of compounds **9** to **35** using the same procedure as described for compound **8** of Example 1. Characterization data are presented in Tables 2a and 2b.

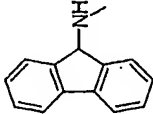


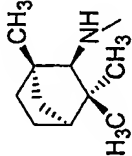
Table 2a

Characterization of Compounds Prepared in Examples 2-28




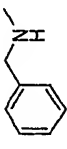
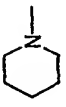
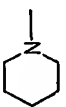

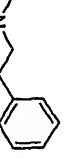
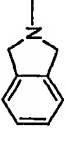

| Ex. | Cpd | Y | X | Name | Characterization | Schm. |
|-----|-----|---|-----------------|--|---|-------|
| 2 | 9 | | NH ₂ | 4-[(4-amino-6-morpholin-4-yl)-[1,3,5]-triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide | ¹ H NMR (CDCl ₃) δ (ppm): 8.02 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.31 (m, 1H), 7.08 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.82 (t, J = 6.7 Hz, 2H), 5.62 (t, J = 5.9 Hz, 1H), 4.90 (bs, 2H), 4.61 (d, J = 6.0 Hz, 2H), 3.75-3.62 (m, 10H). | 1A |
| 3 | 10 | | NH ₂ | 4-{[4-amino-6-(1-indanyl)-amino]-[1,3,5]-triazin-2-ylamino)-N-(2-methyl)-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.05-7.95 (m, 2H), 7.55-7.45 (m, 2H), 7.37-7.10 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.55 (m, 5H), 4.75-4.60 (m, 3H), 3.05-2.75 (m, 2H), 2.60-2.45 (m, 1H), 2.00-1.84 (m, 1H). HRMS (calc.): 466.2229, (found): 466.2225 | 1A |



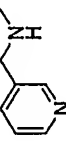
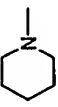
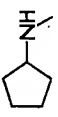
| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|---|---|---|--|------|
| 4 | 11 |  | NH ₂ | N-(2-Amino-phenyl)-4-{[4-amino-6-(4-phenyl)-phenyl]-piperazin-1-yl}-[1,3,5]triazin-2-ylamino]-methyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): mixture of rotamers, 9.05-9.00 (m, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.93 (s), 7.84 (d, J = 8.0 Hz), 7.72 (d, J = 8.2 Hz), 7.58-7.40 (m, 3H), 7.31-7.19 (m, 3H), 7.12-7.05 (m), 6.98 (d, J = 8.1 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 6.80 (t, J = 7.1 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 6.57-6.50 (m, 1H), 5.78-5.60 (m, 2H), 4.67-4.64 (m, 2H), 3.88-3.84 (m, 4H), 3.14 (s, 4H). HRMS (calc.): 477.2389 [M ⁺ - NH ₄], (found): 477.2383 | 1A |
| 5 | 12 |  | NH ₂ | 4-{[4-amino-6-(2-pyridinyl-methyl)-amino]-[1,3,5]-triazin-2-ylamino]-methyl}-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.08 (bs, 1H), 8.51 (bs, 1H), 8.05-7.90 (m, 2H), 7.80-7.60 (m, 1H), 7.55-7.15 (m, 5H), 7.04 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85-6.55 (m, 1H), 5.84 (bs, 2H), 4.75-4.60 (m, 4H). HRMS (calc.): 441.2025, (found): 441.2029 | 1A |
| 6 | 13 |  |  | 4-{[4,6-bis-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-methyl}-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.08 (bs, 1H), 8.05-7.95 (m, 2H), 7.56-7.44 (m, 2H), 7.34 (bd, J = 7.7 Hz, 1H), 7.27-7.10 (m, 8H), 7.04 (td, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.90 (m, 3H), 4.90-4.58 (m, 6H), 3.40-2.80 (m, 4H). HRMS (calc.): 582.2855, (found): 582.2838 | 1B |

| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|---|-----------------|---|--|------|
| 7 | 14 |  | NH ₂ | 4-{[4-Amino-6-(9H-fluoren-9-ylamino)-[1,3,5]triazin-2-ylamino]-N-(2-methyl)-N-(2-amino-phenyl)-benzamide} | ¹ H NMR (acetone-d ₆) δ (ppm): 9.05-9.00 (m, 1H), 8.03-7.87 (m, 2H), 7.80-7.70 (m, 2H), 7.63-7.20 (m, 9H), 7.00 (t, 1H), 6.86 (d, 1H), 6.66 (t, 1H), 6.50-5.50 (m, 6H), 4.75-4.55 (m, 3H). HRMS (calc.): 514.2229, (found): 514.2232 | 1B |
| 8 | 15 |  | NH ₂ | N-(2-amino-phenyl)-4-[(4-amino-6-piperidin-1-yl-[1,3,5]-triazin-2-ylamino)-methyl]-benzamide | ¹ H NMR (CDCl ₃) δ (ppm): 7.96 (bs, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.08 (dt, J = 7.7 Hz, 1.4 Hz, 1H), 6.83 (t, J = 6.6 Hz, 2H), 5.47 (bs, 1H), 4.80 (bs, 2H), 4.60 (d, J = 6.0 Hz, 2H), 3.88 (bs, 2H), 3.67 (t, J = 5.2 Hz, 4H), 1.66-1.58 (m, 2H), 1.56-1.48 (m, 4H). | 1A |
| 9 | 16 |  | NH ₂ | 4-{[4-amino-6-cyclopentyl-amino-[1,3,5]-triazin-2-yl-amino)-methyl]-N-(2-amino-phenyl)-benzamide} | ¹ H NMR (CDCl ₃) δ (ppm): 7.97 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.39-7.34 (m, 3H), 7.10 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.85 (t, J = 7.0 Hz, 2H), 5.56 (bs, 1H), 4.90 (bs, 3H), 4.62 (s, 2H), 4.25-4.19 (m, 1H) 3.88 (bs, 2H), 1.95 (m, 2H), 1.71-1.59 (m, 4H), 1.43-1.37 (m, 2H). | 1A |
| 10 | 17 |  | NH ₂ | (1R)-4-{[4-amino-6-(2-exo-fenethyl-amino)-[1,3,5]-triazin-2-ylamino]-N-(2-methyl)-N-(2-amino-phenyl)-benzamide} | ¹ H NMR (acetone-d ₆) δ (ppm): 9.08 (bs, 1H), AB system (δ _A = 8.00, δ _B = 7.51, J = 8.0 Hz, 4H), 7.33 (bd, J = 7.7 Hz, 1H), 7.03 (ddd, J = 8.0 Hz, 7.3 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.60-6.28 (m, 1H), 5.80-5.20 (m, 3H), 4.67 (bs, 4H), 3.87 (bd, J = 9.1 Hz, 1H), 1.80-1.60 (m, 4H), 1.56-1.42 (m, 1H), 1.34-1.00 (m including 2 s, 8H), 0.84 (s, 3H). HRMS (calc.): 486.2855, (found): 486.2844 | 1A |

| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|---|---|---|--|------|
| 11 | 18 | | | 4-{[4-allyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-N-(2-methyl)-N-(2-amino-phenyl)-benzamide} | ¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.4 Hz, 2H), 7.58-7.42 (m, 2H), 7.34 (bd, J = 8.0 Hz, 1H), 7.27-7.10 (m, 4H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.60-5.70 (m, 3H), 5.26-5.00 (m, 2H), 4.86-4.54 (m, 4H), 4.10-3.90 (m, 2H), 3.38-3.10 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 506.2542, (found): 506.2533 | 1B |
| 12 | 19 | | | 4-{[4-cyclopropyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-N-(2-methyl)-N-(2-amino-phenyl)-benzamide} | ¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.00 (bd, J = 7.7 Hz, 2H), 7.60-7.40 (m, 2H), 7.33 (dd, J = 7.8 Hz, 1.3 Hz, 1H), 7.28-7.10 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (dd, J = 7.8 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.3 Hz, 1H), 6.67-5.80 (m, 2H), 4.90-4.50 (m, 4H), 3.40-3.10 (m, 2H), 3.05-2.70 (m, 3H), 0.75-0.43 (m, 4H). HRMS (calc.): 506.2542, (found): 506.2548 | 1B |
| 13 | 20 | | | 4-{[4-Amino-6-phenethylamino-[1,3,5]-triazin-2-ylamino]-N-(2-methyl)-N-(2-amino-phenyl)-benzamide} | ¹ H NMR (acetone-d ₆) δ (ppm): 9.03 (s, 1H), 7.97 (d, J = 7.7 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.99 (td, J = 8.0 Hz, 1.3 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.3 Hz, 1H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.62-5.40 (m, 5H), 4.75-4.45 (m, 3H), 3.59-3.45 (m, 2H), 2.95-2.70 (m, 2H). HRMS (calc.): 454.2229, (found): 454.2235 | 1A |

| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|---|-----------------|---|--|------|
| 14 | 21 | | NH ₂ | N-(2-Amino-phenyl)-4-([4-amino-6-(3,4,5-trimethoxyphenylamino)-2-ylamino]-methyl)-benzamide | ¹ H NMR (CDCl ₃ /MeOD) δ (ppm): 7.72 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 7.7 Hz, 1H), 6.91 (td, J = 7.7 Hz, 1.2 Hz, 1H), 6.70-6.61 (m, 4H), 4.61 (bs, 2H), 3.58-3.52 (m, 9H). | 1B |
| 15 | 22 | | NH ₂ | 4-([4-Amino-6-(2,3-dihydroindol-1-yl)-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide | ¹ H NMR (CDCl ₃ /MeOD) δ (ppm): 8.06 (bs, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 7.06 (d, J = 7.4 Hz, 1H), 7.02-6.96 (m, 2H), 6.84-6.71 (m, 3H), 4.61 (bs, 2H), 4.03 (t, J = 8.5 Hz, 2H), 3.02 (t, J = 8.5 Hz, 2H). | 1B |
| 16 | 23 | | NH ₂ | 4-([4-Amino-6-[2-(2-methoxyphenyl)-ethylamino]-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): mixture of rotamers, 9.06 (s, 1H), 7.96 (d, J = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.21-6.70 (m, 6H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-5.70 (m, 5H), 4.75-4.55 (m, 3H), 3.81 (s, 3H), 3.55-3.45 (m, 2H), 2.90-2.78 (m, 2H). HRMS (calc.): 484.2335, (found): 484.2331 | 1A |
| 17 | 24 | | NH ₂ | 4-([4-Amino-6-[2-(2-fluorophenyl)-ethylamino]-[1,3,5]triazin-2-ylamino]-methyl)-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): mixture of rotamers, 9.03 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.38-7.17 (m, 2H), 7.17-6.95 (m, 4H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (t, J = 7.0 Hz, 1H), 6.50-5.60 (m, 5H), 4.75-4.55 (m, 3H), 3.60-3.52 (m, 2H), 2.95-2.85 (m, 2H). HRMS (calc.): 472.2135, (found): 472.2146 | 1A |

| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|---|---|--|--|------|
| 18 | 25 |  |  | 4-{{[4-benzyl-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-ylamino]-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.06 (bs, 1H), 8.04-7.93 (m, 2H), 7.57-7.12 (m, 12H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.91 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.72 (bt, J = 7.6 Hz, 1H), 6.68-5.90 (m, 3H), 4.84-4.50 (m, 7H), 3.35-3.13 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 556.2699, (found): 556.2706 | 1B |
| 19 | 26 |  |  | N-(2-Amino-phenyl)-4-[(4,6-di-piperidin-1-yl)-[1,3,5]triazin-2-ylamino)-N-(2-amino-phenyl)-benzamide | ¹ H NMR: (CDCl ₃) δ (ppm): 7.83 (d, J = 8.2 Hz, 3H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, J = 5.4 Hz, 8H), 1.63-1.53 (m, 12H). | 1B |
| 20 | 27 |  |  | 4-{{[6-(2-indanylamino)-4-phenethyl-amino-[1,3,5]-triazin-2-ylamino]-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.05-7.90 (m, 2H), 7.60-7.40 (m, 2H), 7.35-7.05 (m, 10H), 7.04 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.71 (t, J = 7.3 Hz, 1H), 6.60-5.70 (m, 3H), 4.95-4.50 (m, 5H), 3.70-2.80 (m, 8H). HRMS (calc.): 552.2750 [M ⁺ - NH ₄], (found): 552.2746 | 1B |
| 21 | 28 |  |  | 4-{{[4-benzyl-amino-6-(2-indanylamino)-[1,3,5]-triazin-2-ylamino]-N-(2-amino-phenyl)-benzamide | ¹ H NMR (CDCl ₃) δ (ppm): 7.83 (d, J = 8.2 Hz, 3H), 7.44 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.4, 1H), 7.12-7.06 (m, 1H), 6.87-6.82 (m, 2H), 5.11 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.3 Hz, 2H), 3.87 (bs, 2H), 3.69 (t, J = 5.4 Hz), 1.63-1.53 (m, 12H). | 1A |

| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|--|--|--|--|------|
| 22 | 29 |  | NH ₂ | 4-[(4-Amino-6-benzylamino-[1,3,5]triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.04 (s, 1H), 7.95 (d, J = 7.3 Hz, 2H), 7.45 (d, J = 7.1 Hz, 2H), 7.38-7.15 (m, 6H), 7.00 (td, J = 8.0 Hz, 1.5 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.67-6.25 (m, 3H), 5.85-5.55 (m, 3H), 4.61 (d, J = 6.3 Hz, 2H), 4.54 (d, J = 5.2 Hz, 2H). HRMS (calc.): 440.2073, (found): 440.2078 | 1A |
| 23 | 30 |  |  | 4-[(6-(2-indanyl-amino)-4-(3-pyridinyl-methyl-amino)-[1,3,5]-triazin-2-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): mixture of rotamers, 9.20-9.00 (m, 1H), 8.70-8.35 (m, 2H), 8.05-7.90 (m, 2H), 7.85-7.55 (m, 1H), 7.55-7.10 (m, 8H), 7.04 (dt, J = 7.6 Hz, 1.5 Hz, 1H), 6.91 (bd, J = 7.4 Hz, 1H), 6.71 (bt, J = 7.3 Hz, 1H), 6.80-6.00 (m, 3H), 4.84-4.50 (m, 7H), 3.34-3.12 (m, 2H), 3.00-2.80 (m, 2H). HRMS (calc.): 539.2546 [M ⁺ - NH ₄], (found): 539.2533 | 1B |
| 24 | 31 |  |  | N-(2-Amino-phenyl)-4-[(4-piperidin-1-yl-6-pyrrolidin-1-yl)-[1,3,5]triazin-2-ylamino)-methyl]-benzamide | ¹ H NMR (CDCl ₃) δ (ppm): 7.89 (bs, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 1H), 7.09 (dt, J = 7.7 Hz, 1.6 Hz, 1H), 6.87-6.82 (m, 2H), 4.83 (bs, 1H), 4.62 (d, J = 6.0 Hz, 2H), 4.24 (m, 1H), 3.88 (bs, 1H), 2.04-1.96 (m, 2H), 1.70-1.52 (m, 10H), 1.46-1.38 (m, 2H). | 1B |


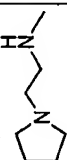
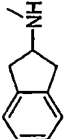

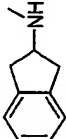
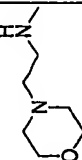
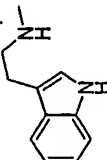
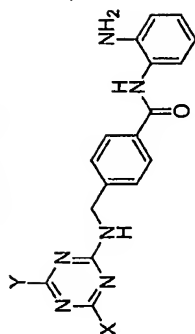
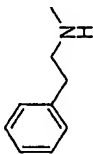
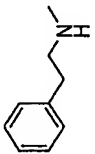
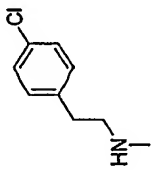
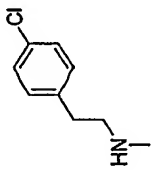

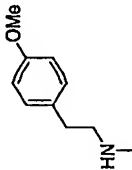

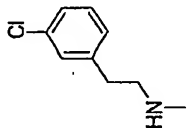

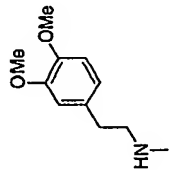

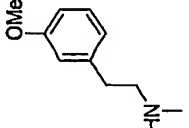
| Ex. | Cpd | Y | X | Name | Characterization | Schm |
|-----|-----|---|--|--|---|------|
| 25 | 32 |  |  | N-(2-Amino-6-(2-pyrrolidin-1-yl)-ethylamino)-pyrimidin-4-ylmethylbenzamide | ¹ H NMR (CDCl ₃) δ (ppm): 8.27 (bs, 1H), 7.74 (d, J = 7.4 Hz, 2H), 7.29 (m, 3H), 7.05 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.81-6.76 (m, 2H), 5.62 (bs, 2H), 4.57 (bs, 2H), 3.91 (bs, 2H), 3.69 (m, 4H), 3.45 (m, 2H), 2.57 (t, J = 6.2 Hz, 2H), 2.47 (m, 4H), 1.71 (m, 4H), 1.59-1.50 (m, 6H). | 1B |
| 26 | 33 |  |  | 4-{[6-(2-amino-6-(2-pyrrolidin-1-yl)-ethylamino)-pyrimidin-4-ylmethyl]-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.08-7.95 (m, 2H), 7.60-7.43 (m, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 6.72 (t, J = 7.4 Hz, 1H), 6.55-6.05 (m, 2H), 4.86-4.60 (m, 5H), 3.80-3.56 (m, 8H), 3.38-3.12 (m, 2H), 3.04-2.82 (m, 2H). | 1B |
| 27 | 34 |  |  | N-(2-Amino-6-(2-pyrrolidin-1-yl)-ethylamino)-pyrimidin-4-ylmethylbenzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.08 (bs, 1H), 8.01 (bd, J = 7.4 Hz, 2H), 7.56-7.43 (m, 2H), 7.33 (bd, J = 8.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.04 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.90 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.71 (dt, J = 7.6 Hz, 1.4 Hz, 1H), 6.65-5.75 (m, 2H), 4.90-4.58 (m, 5H), 3.66-2.34 (m, 16H). | 1B |
| 28 | 35 |  | NH ₂ | 4-{[6-(2-amino-6-(2-pyrrolidin-1-yl)-ethylamino)-pyrimidin-4-ylmethyl]-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 10.00 (s, 1H), 9.13 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.70-7.50 (m, 1H), 7.50-7.22 (m, 4H), 7.18-6.91 (m, 4H), 6.85 (d, J = 7.1 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.40-5.90 (m, 3H), 4.75-4.50 (m, 2H), 4.37 (s, 2H), 3.62 (d, J = 6.3 Hz, 2H), 2.99 (s, 2H). | 1A |


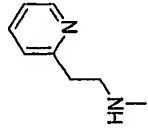

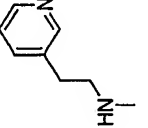
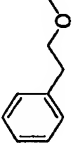

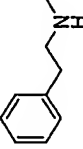
Table 2b


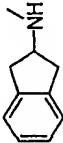



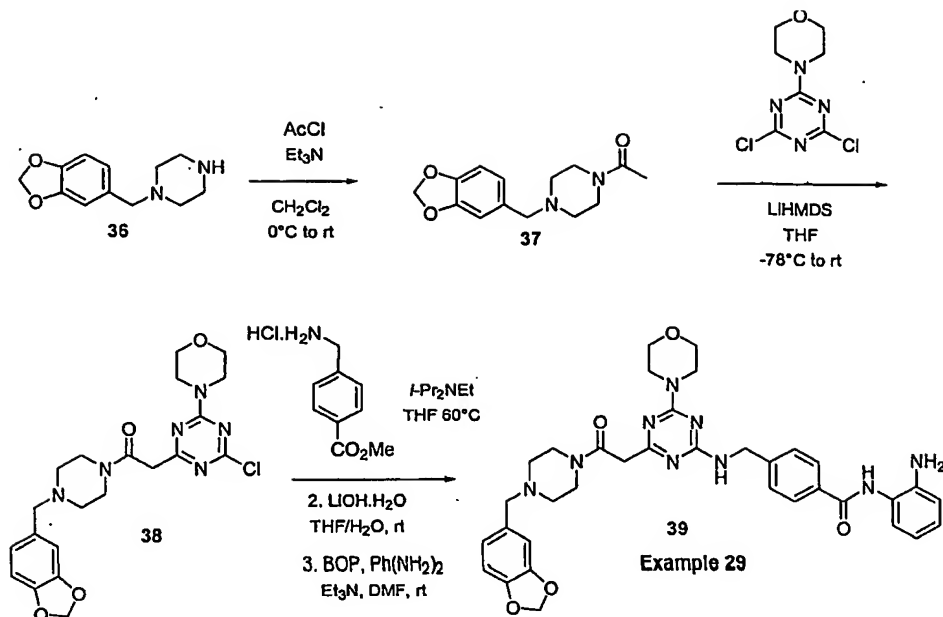
| Ex. | Cpd | X | Y | Name | Characterization | Schm |
|-----|-----|---|-----------------|---|---|------|
| 329 | 470 | | NH ₂ | 4-{[4-amino-6-(3-phenyl-propyl-1-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.03 (s, 1H), 7.96 (d, J=8.2 Hz, 2H), 7.46 (d, J=7.7 Hz, 2H), 7.35-7.10 (m, 6H), 7.00 (t, J=7.7 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 6.67 (t, J=7.7 Hz, 1H), 6.60-5.40 (m, 6H), 4.62 (s, 2H), 3.35 (dd, J=12.1, 6.9 Hz, 2H), 2.75-2.60 (m, 2H), 1.95-1.80 (m, 2H). | 1A |
| 330 | 471 | | | N-(2-amino-phenyl)-4-{[4-cyclopropyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.04 (s, 1H), 7.96 (d, J=8.0 Hz, 2H), 7.55-7.40 (m, 2H), 7.35-7.10 (m, 6H), 6.98 (t, J=7.4 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (t, J=7.3 Hz, 1H), 6.20-5.50 (m, 3H), 4.80-4.50 (m, 4H), 3.65-3.45 (m, 2H), 3.00-2.60 (m, 2H), 0.80-0.40 (m, 4H). | 1B |
| 331 | 472 | | | N-(2-amino-phenyl)-4-{[4-cyclopropyl-methylamino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.06 (bs, 1H), 8.00 (bd, J = 7.1, 2H), 7.50 (bs, 1H), 7.33 (d, J = 6.6 Hz, 1H), 7.28-7.07 (m, 4H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.55-5.70 (m, 3H), 4.90-4.50 (m, 5H), 3.40-2.80 (m, 6H), 1.07 (bs, 1H), 0.44 (bs, 2H), 0.23 (bs, 2H). | 1B |

| Ex. | Cpd | X | Y | Name | Characterization | Schm |
|-----|-----|---|---|---|---|------|
| 332 | 473 |  | <i>n</i> -BuNH | <i>N</i> -(2-amino-phenyl)-4-[(4- <i>n</i> -butyl-amino-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.08 (s, 1H), 7.83 (d, J = 6.6 Hz, 2H), 7.45-7.05 (m, 8H), 7.08 (td, J = 7.8, 1.5 Hz, 1H), 6.84 (t, J = 8.1 Hz, 2H), 6.70-5.00 (m, 3H), 4.70-4.50 (m, 2H), 3.65-3.50 (m, 2H), 3.45-3.25 (m, 2H), 2.40-2.25 (m, 2H), 1.60-1.45 (m, 2H), 1.45-1.00 (m, 2H), 1.00-0.8 (m, 3). | 1B |
| 333 | 474 |  | MeOCH ₂ CH ₂ NH | <i>N</i> -(2-amino-phenyl)-4-[(4-(2-methoxy-ethyl)-1-amino)-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.02 (s), 8.58 (s), 8.40 (dd, J = 7.2, 2 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.51-7.40 (m, 2H), 7.70-6.90 (m, 7H), 6.86 (dd, J = 8.1, 1.2 Hz), 6.76 (dd, J = 7.5, 1.8 Hz), 6.67 (td, J = 7.8, 1.5 Hz), 6.60-5.50 (m, 3H), 4.75-4.55 (m, 4H), 3.65-3.35 (m, 6H), 3.35-3.20 (s, 3H), 2.95-2.75 (m, 2H). | 1B |
| 334 | 475 |  |  | <i>N</i> -(2-amino-phenyl)-4-[(4-(4-chloro-phenethyl-amino)-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.02 (s, 1H), 8.02-7.91 (m, 2H), 7.58-7.40 (m, 2H), 7.28 (s, 4H), 7.20-7.05 (m, 1H), 6.99 (td, J = 7.5, 1.8 Hz, 1H), 6.86 (d, J = 7.8 Hz, 1H), 6.67 (t, J = 6.9 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.65-3.40 (bs, 2H), 2.95-2.65 (m, 2H), 0.75-0.55 (m, 2H), 0.55-0.40 (m, 2H). | 1B |
| 335 | 476 |  |  | <i>N</i> -(2-amino-phenyl)-4-[(6-cyclopropyl-amino-4-(4-methoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.55-7.72 (m, 4H), 7.55-6.75 (m, 9H), 6.75-5.30 (m, 3H), 4.69 (m, 2H), 3.85 (s, 3H), 3.63 (bs, 2H), 2.86 (m, 3H), 0.85 (bs, 2H), 0.61 (bs, 2H). | 1B |

| Ex. | Cpd | X | Y | Name | Characterization | Schm |
|-----|-----|---|--|---|---|------|
| 336 | 477 |  |  | N-(2-amino-phenyl)-4-{{[4-(3-chloro-phenethyl-amino)-6-cyclopropyl-amino-[1,3,5]triazin-2-yl-amino]-methyl}}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.03 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.60-7.37 (m, 2H), 7.37-7.12 (m, 5H), 6.99 (t, J = 6.9 Hz, 1H), 6.86 (d, J = 6.9 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.67-3.45 (m, 2H), 3.00-2.67 (m, 3H), 0.75-0.40 (m, 4H). | 1B |
| 337 | 478 |  |  | N-(2-amino-phenyl)-4-{{[6-cyclopropyl-amino-4-(3,4-dimethoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.29 (d, J = 8.1 Hz, 1H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), 6.95-6.72 (m, 4H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.20-5.60 (m, 3H), 4.78-4.52 (m, 4H), 3.75 (s, 6H), 3.65-3.42 (m, 2H), 2.95-2.65 (m, 3H), 0.72-0.40 (m, 4H). | 1B |
| 338 | 479 |  |  | N-(2-amino-phenyl)-4-{{[6-cyclopropyl-amino-4-(3-methoxy-phenethyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.02 (s, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.60-7.35 (m, 2H), 7.29 (d, J = 7.5 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.99 (td, J = 7.5, 1.5 Hz, 1H), 6.90-6.70 (m, 4H), 6.67 (t, J = 7.8 Hz, 1H), 6.60-5.60 (m, 3H), 4.77-4.50 (m, 4H), 3.76 (s, 3H), 3.65-3.45 (m, 2H), 2.92-2.65 (m, 3H), 0.72-0.42 (m, 4H). | 1B |

| Ex. | Cpd | X | Y | Name | Characterization | Schm |
|-----|-----|---|---|--|--|-------|
| 339 | 480 |  |  | N-(2-amino-phenyl)-4-[(6-cyclopropyl-amino-4-(2-pyridin-2-yl-ethyl-1-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.03 (s, 1H), 8.50 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.60-7.40 (m, 2H), 7.35-7.08 (m, 3H), 6.99 (td, J = 8.1, 1.5 Hz, 1H), 6.67 (td, J = 7.8, 1.5 Hz, 1H), 6.60-5.60 (m, 3H), 4.75-4.50 (m, 4H), 3.80-3.60 (m, 2H), 3.15-2.90 (m, 2H), 2.90-2.65 (m, 1H), 0.73-0.40 (m, 4H). | 1B |
| 340 | 481 |  |  | N-(2-amino-phenyl)-4-[(6-cyclopropyl-amino-4-(3-pyridin-2-yl-ethyl-1-amino)-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.20-9.00 (m, 1H), 8.70-8.50 (m, 2H), 8.00 and 7.88 (2d, J = 7.9 Hz, 2H), 7.75-7.43 (m, 3H), 7.38-6.67 (m, 5H), 6.22-5.78 (m, 3H), 4.80-4.55 (m, 4H), 3.61 (bs, 2H), 3.20-2.65 (m, 3H), 0.80-0.45 (m, 4H). | 1B |
| 341 | 482 |  |  | N-(2-amino-phenyl)-4-[(6-cyclopropyl-amino-6-phenethyl-oxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): 9.04 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.60-7.40 (m, 2H), 7.35-7.15 (m, 6H), 7.00 (td, J = 7.5, 1.5 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 7.18-6.35 (m, 2H), 4.75-4.30 (m, 6H), 3.10-2.92 (m, 2H), 0.75-0.63 (m, 2H), 0.57-0.48 (m, 2H). | 1, 25 |
| 342 | 483 |  | Me | N-(2-amino-phenyl)-4-[(6-methyl-4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide | ¹ H NMR (300 MHz, acetone-d ₆ + ε DMSO-d ₆) δ (ppm): mixture of rotamers, 9.62 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.80-7.44 (m, 3H), 7.40-7.10 (m, 8H), 7.01 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 4.85 (bs, 2H), 4.72-4.54 (m, 2H), 3.63-3.42 (m, 2H), 2.96-2.74 (m, 2H), 2.21 and 2.13 (2s, 3H). | 30 |

| Ex. | Cpd | X | Y | Name | Characterization | Schm |
|-----|-----|---|---|---|---|------|
| 343 | 484 |  | NH ₂ | N-(2-amino-phenyl)-4-{[4-amino-6-phenyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): mixture of rotamers, 9.08 (bs, 1H), 8.48-8.36 (m, 2H), 8.02 (d, J = 8.2 Hz, 2H), 7.63-7.42 (m, 5H), 7.33 (d, J = 7.7 Hz, 1H), 7.19 (bs, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.70 (t, J = 7.6 Hz, 1H), 6.35 and 6.25 (2bs, 2H), 4.87 and 4.75 (2d, J = 5.9 Hz, 2H), 4.65 (bs, 2H). | 30 |
| 344 | 485 |  |  | N-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-phenyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide | ¹ H NMR (300 MHz, acetone-d ₆) δ (ppm): mixture of rotamers, 9.14-8.96 (m, 1H), 8.54-8.30 (m, 2H), 8.09-7.95 (m, 2H), 7.68-7.40 (m, 5H), 7.38-7.08 (m, 6H), 7.03 (t, J = 7.3 Hz, 1H), 6.94-6.76 (m, 2H), 6.71 (t, J = 7.3 Hz, 1H), 5.13-4.54 (m, 5H), 3.49-3.18 (m, 2H), 3.12-2.90 (m, 2H). | 30 |



Example 29

N-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-yl]-2-oxo-ethyl]-6-morpholin-4-yl-[1,3,5] triazin-2-ylamino}-methyl)-benzamide (compound 39)

Step 1: *N*-Acetyl-1-piperonylpiperazine (compound 37)

[0175] To a stirred solution at 0°C of 1-piperonylpiperazine 36 (5.00 g, 22.7 mmol) in anhydrous CH₂Cl₂ (60 mL) was added Et₃N (6.33 mL, 45.4 mmol) followed by acetyl chloride (1.94 mL, 27.2 mmol). The reaction mixture was stirred 30 min. at 0°C and then 2 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 4/96) to afford the title compound 37 (5.52 g, 21.11 mmol, 93% yield) as a yellow solid. ¹H NMR: (300 MHz, CDCl₃) δ (ppm): 6.83 (s, 1H), 6.72 (m, 2H), 5.92 (s, 2H), 3.59 (t, J = 5.1 Hz, 2H), 3.44-3.40 (m, 4H), 2.42 (dt, J = 5.1 Hz, 5.1 Hz, 4H), 2.06 (s, 3H).

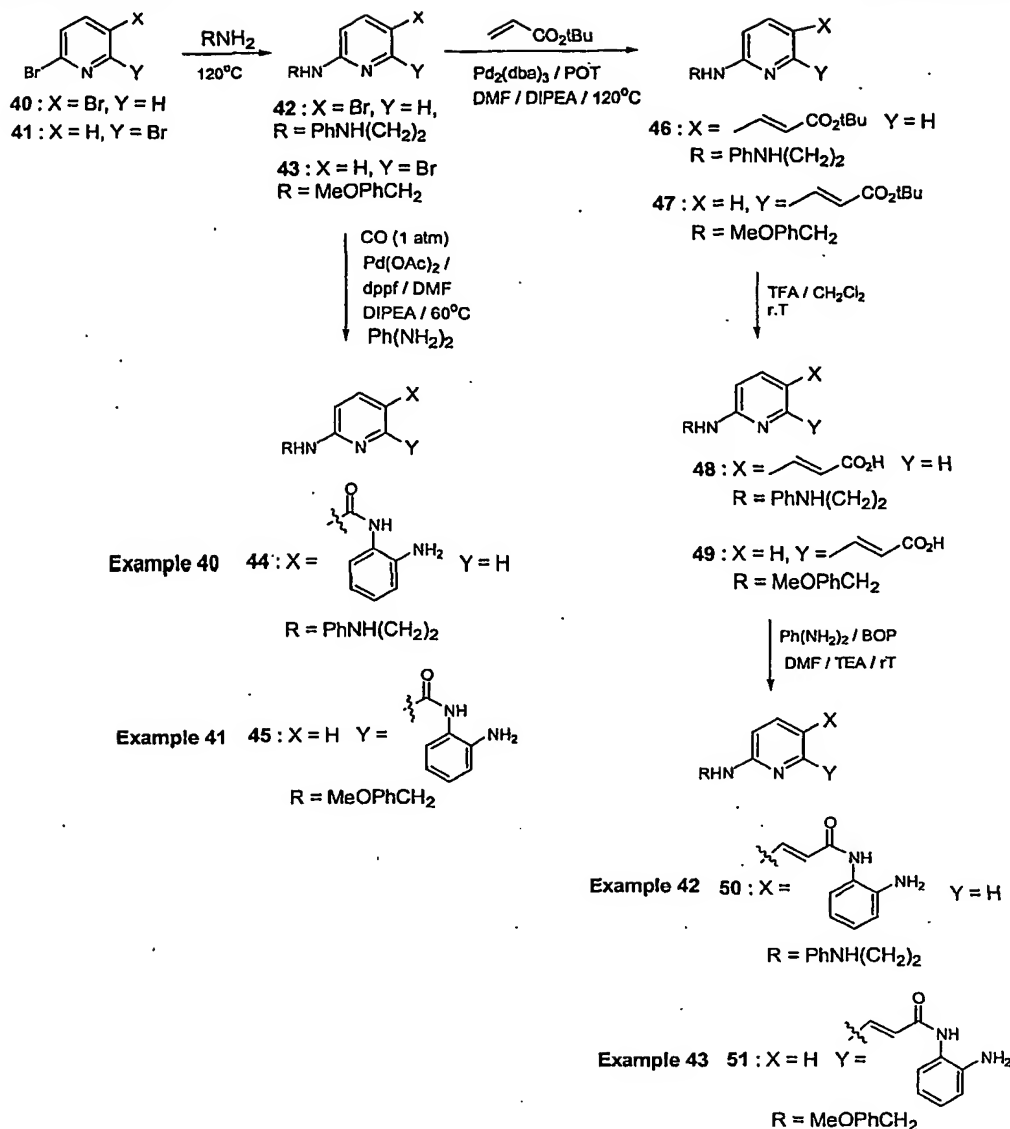
Step 2: 2-Chloro-4-morpholin-4-yl-6-[2-(4-benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-yl]-2-oxo-ethyl]-[1,3,5]triazine (compound 38)

[0176] To a stirred solution of 37 (3.00 g, 11.4 mmol) in anhydrous THF (25 mL) at -78°C was slowly added a solution of LiHMDS (11.4 mL,

11.4 mmol, 1 M in THF). The reaction mixture was stirred 1 h at -78°C and a solution of 2,4-dichloro-6-morpholin-4-yl-[1,3,5]triazine (2.69 g, 11.4 mmol) in anhydrous THF (25 mL) was added. The reaction mixture was slowly warmed up at room temperature and the reaction was quenched after 16 h with a saturated aqueous solution of NH_4Cl . The THF was evaporated and the residue was diluted with AcOEt. The organic layer was successively washed with sat. NH_4Cl and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$: 1/99 \rightarrow 3/97) to afford the title compound 38 (4.84 g, 10.49 mmol, 92% yield) as a pale yellow solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 6.84 (s, 1H), 6.77-6.69 (m, 2H), 5.95 (s, 2H), 3.75-3.43 (m, 16H), 2.42 (m, 4H).

Step 3: N-(2-Amino-phenyl)-4-({4-[2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-2-oxo-ethyl]-6-morpholin-4-yl-[1,3,5]triazin-2-ylamino}-methyl)-benzamide (compound 39)

[0177] The title compound 39 was obtained following the same procedure as Example 1, step 5. ^1H NMR (CDCl_3) δ (ppm): 7.96 (bs, 1H), 7.87 (d, $J = 8.2$ Hz, 2H), 7.39 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 1H), 7.10 (dt, $J = 7.6$ Hz, 1.2 Hz, 1H), 6.87-6.81 (m, 3H), 6.75-6.68 (m, 2H), 5.93 (s, 2H), 5.67 (bs, 1H), 4.64 (s, 2H), 3.90 (bs, 2H), 3.75-3.35 (m, 16H), 2.45-2.30 (m, 4H).



Example 40

N-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound 44)

Step 1: *N*-(5-Bromo-pyridin-2-yl)-*N'*-phenyl-ethane-1,2-diamine (compound 42)

[0178] A mixture of 2,5-dibromopyridine 40 (2.08 g, 8.6 mmol) and phenyl-1,2-ethyldiamine (1.98 g; 14.6 mmol, 1.7 equiv.) was stirred under nitrogen at 120°C for 6h. After cooling down to room temperature, the solid mixture was ground in a mortar, dissolved in ethyl acetate (200 mL), washed with saturated NaHCO₃ (2 x 50 mL), dried (MgSO₄), filtered and concentrated. After a quick purification through a short chromatographic column (silica gel, elution 50% ether

in hexanes), a pale yellow solid **42** (1.75 g, 6.01 mmol, 70% yield) was obtained. ^{13}C NMR (300 MHz, acetone- d_6) δ (ppm): 158.6, 149.6, 148.8, 139.9, 129.8, 117.1, 113.1, 110.8, 106.6, 43.9, 41.5. LMRS = 294.0 (M+1).

Step 2: *N*-(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide (compound **44**)

[0179] A mixture of 5-bromo-2-*N*-alkanyl-2-aminopyridine **42** (352 mg, 1.2 mmol), 1,2-phenylenediamine (3.95 mmol, 3.3 equiv.), $\text{Pd}(\text{OAc})_2$ (0.31 mmol, 26% mol) and 1,1'-bis (diphenylphosphino) ferrocene (124 mg, 0.22 mmol) was suspended in degassed DMF (3mL), treated with diisopropylethyl amine (0.9 mL, 5.2 mmol) and the system flushed with CO. The reaction mixture was warmed up to 60°C and stirred under CO (balloon) for 18 h at this temperature. After evaporation of the DMF under vacuo, the residue was purified through a chromatographic column (silica gel, elution 3% to 6% methanol in dichloromethane) to give 258 mg (0.74 mmol, 62 % yield) of the aminoanilide **44**. ^1H -NMR ($\text{CD}_3\text{OD}-d_4$), δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt, J = 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H).

Example 41

N-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide (compound **45**)

Step 1: *N*-(5-Bromo-pyridin-2-yl)-4-methoxybenzylamine (compound **43**)

[0180] A mixture of 2,6-dibromopyridine **41** (6.03 mmol, 2 equiv.) and para-methoxybenzyl amine (413 mg, 3.01 mmol) was stirred under nitrogen at 120°C for 6h. After identical work-up procedure described before and purification through a pad of silica gel (elution 50% ether in hexanes), a pale yellow solid **43** (773 mg, 2.60 mmol, 87% yield) was obtained. ^{13}C NMR (300 MHz, CDCl_3) δ (ppm): 159.1, 139.7, 132.1, 130.5, 128.9, 127.2, 116.2, 114.3, 104.8, 55.4, 46.0. LMRS = 295.0 (M+1).

Step 2: N-(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide
(compound 45)

[0181] Following the procedure described in Example 40, step 2, but substituting 43 for 42, the title compound 45 was obtained in 61% yield.

Example 42

N-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound 50)

Step 2: 3-[6-(2-Phenylamino-ethylamino)-pyridin-3-yl]-acrylic acid
tert-butyl ester (compound 46)

[0182] In a 50 mL flask, a mixture of 42 (308 mg, 1.05 mmol), tert-butylacrylate (0.8 mL, 5.5 mmol), diisopropylethylamine (0.8 mL, 4.6 mmol), tri-*o*-tolylphosphine (POT, 192 mg, 0.63 mmol), Pd₂(dba)₃ (73 mg, 0.08 mmol) in anhydrous DMF (4 mL) was stirred at 120°C (preheated oil bath) for 2h under nitrogen. After DMF removal, the crude residue was submitted to a chromatographic purification (column silica gel, 50% ether in hexanes) to afford 316 mg of 46 (88% yield). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 166.6, 159.3, 149.6, 147.8, 140.7, 134.9, 129.1, 119.8, 117.3, 115.9, 112.6, 107.8, 80.0, 43.5, 40.9, 28.1. LRMS = 340.3 (M+1).

Step 3: 3-[6-(2-Phenylamino-ethylamino)-pyridin-3-yl]-acrylic acid
(compound 48)

[0183] Ester 46 (0.93 mmol) was dissolved 40 % TFA in dichloromethane (10 mL) and the solution stirred at room temperature overnight. The solvent was removed under vacuo distilling with acetonitrile (3x10 mL) and stored under high vacuum for 6h. The solid residue 48 was employed for the next reaction without further purification. LRMS = 284.1 (M+1).

Step 4: N-(2-aminophenyl)-3-[6-(2-phenylamino-ethylamino)-pyridin-3-yl]-acrylamide (compound 50)

[0184] A mixture of acid 48 (0.93 mmol), BOP (495 mg, 1.12 mmol) and 1,2-phenylenediamine (124 mg, 1.15 mmol) were dissolved in dry acetonitrile (4 mL) and treated with triethylamine (0.8 mL, 5.7 mmol). The solution was stirred under nitrogen at room temperature for 16h. After concentration under vacuo, the crude was purified through chromatographic column (5% methanol in dichloromethane), then was

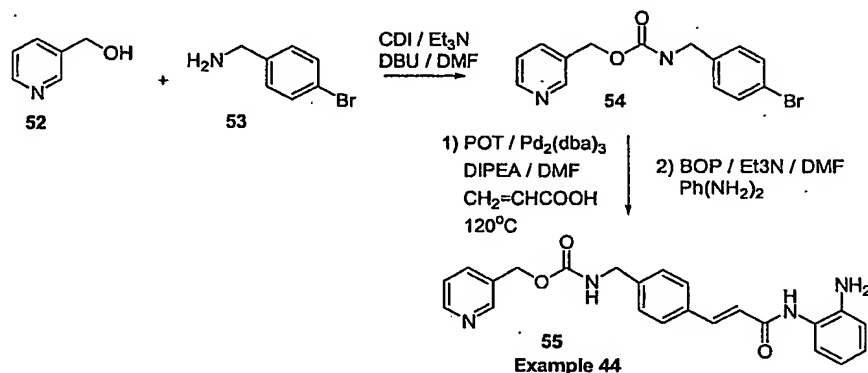
crystallized from chloroform to give 50 (247 mg, 71% yield). $^1\text{H-NMR}$ (DMSO- d_6), δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J = 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H).

Example 43

N-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound 51)

Step 2: *N*-(2-aminophenyl)-3-[6-(4-methoxy-benzylamino)-pyridin-2-yl]-acrylamide (compound 51)

[0185] Following the procedure described in Example 42, steps 2, 3, 4, but substituting 43 for 42, the title compound 51 was obtained in 50% yield (on 2 steps). $^1\text{H-NMR}$ (CDCl_3), δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H).



Example 44

4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

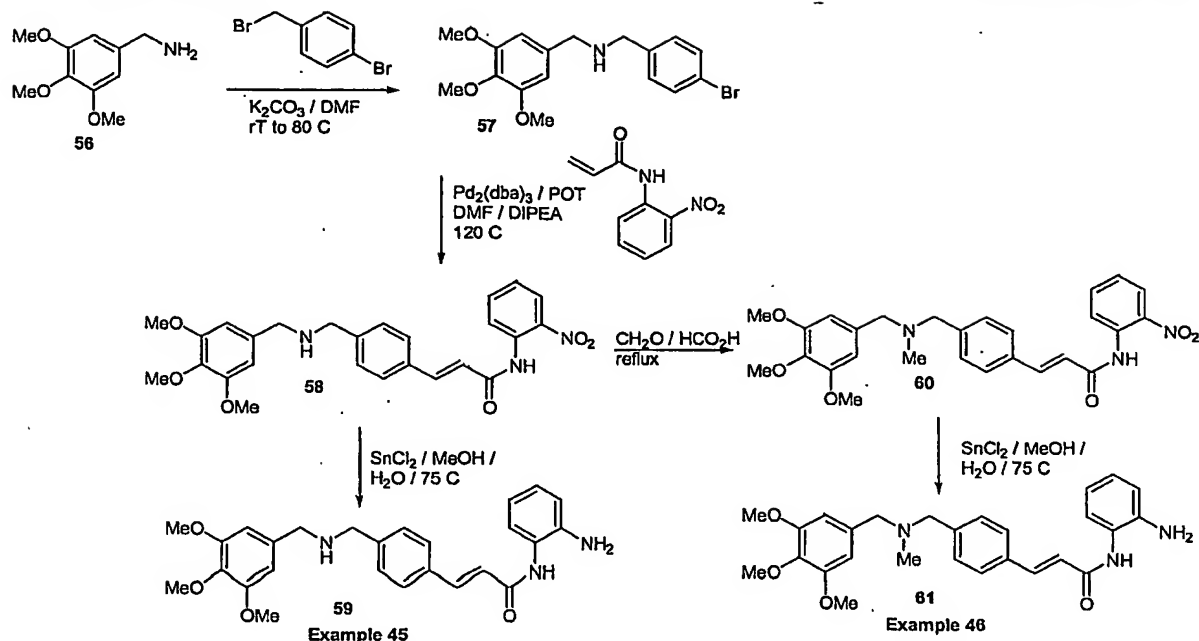
Step 1: (4-bromo-benzyl)-carbamic acid pyridin-3-yl-methyl ester (compound 54)

[0186] 4-bromobenzylamine HCl (3.0g, 13.4 mmol) was dissolved in DMF (60 mL) at rt and then Et_3N (4.13 mL, 29.7 mmol) was added dropwise over 10 min to give cloudy solution. To this, DBU (2.42 mL, 16.2 mmol)

and 1,1'-carbonyl diimidazole (2.41g, 14.8 mmol) were added. After being stirred for 1 h at rt, 3-pyridylcarbinol (1.44 mL, 14.8 mmol) was added dropwise over 10 min. The resulting reaction mixture was stirred overnight and then concentrated under reduced pressure. The residue obtained was diluted with ether/EtOAc (9:1) and then washed with H₂O. The organic layer was dried over Na₂SO₄, filtered and then concentrated to give the crude product which was recrystallized from EtOAc to give 2.55g of product **54** (59% yield, LRMS = 323 (M+1)).

Step 2: 4-[2-(2-amino-phenylcarbamoyl)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester (compound 55)

[0187] Following the procedure described in Example 42, steps 2, 3, but substituting **54** for **42**, and acrylic acid for tert-butyl acrylate the title compound **55** was obtained in an overall yield of 20%. ¹H NMR: (DMSO-d₆) δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d, J = 3.3 Hz, 1H), 7.85 (d, J = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, J = 7.69 Hz, 1H), 6.89 (dd, J = 7.14 Hz, J = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, J = 7.1 Hz, J = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H).



Example 45

N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound 59)

Step 1: (4-Bromo-benzyl)-(3,4,5-trimethoxy-benzyl)-amine (compound 57)

[0188] To a stirred suspension of K_2CO_3 (522 mg, 3.77 mmol) in dry DMF was added 3,4,5-trimethoxybenzylamine (1.10 mL, 6.44 mmol, 2.2 equiv.) followed by a solution of *p*-bromo benzylbromide (0.73 g, 2.91 mmol) in dry DMF (8 mL). The mixture was stirred at room temperature under nitrogen for two days in the dark, diluted with dichloromethane (200 mL), washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by chromatographic column on silica gel (elution 5% methanol in dichloromethane) to give 2.59 mmol (89% yield) of dibenzylamine 57. ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 152.5, 138.8, 136.1, 135.4, 130.6, 129.2, 119.8, 104.2, 59.9, 55.3, 52.6, 51.7. LRMS = 368.4 ($M+1$).

Step 2: *N*-(2-Nitro-phenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (compound 58)

Preparation of the nitroacrylanilide

[0189] To a mixture of 2-nitroaniline (1.73 g, 12.5 mmol), DMAP (321 mg, 2.6 mmol) and 2,6-di-*tert*-butyl-4-methylphenol (308 mg) in dry dichloromethane (50 mL) at 0°C was added triethylamine (10.6 mL, 76

mmol) followed by acryloylchloride (3.2 mL, 38 mmol, 3.0 equiv.), and the mixture was stirred at room temperature for 16h. The solution was diluted with dichloromethane (250 mL), cooled to 0°C and the excess of reagent quenched with saturated NaHCO₃ (stirring for 1 h). The organic layer was then washed (5% KHSO₄, then brine), dried (MgSO₄), filtered and concentrated under reduced pressure. After purification through chromatographic column on silica gel (elution 50% ether in hexanes), 642 mg (3.34 mmol, 27% yield) of the amide was obtained. ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 163.6, 136.0, 135.6, 134.5, 131.3, 128.6, 125.4, 123.1, 121.8. LRMS = 193.2 (M+1).

Step 3: N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxy-benzylamino)-methyl]-phenyl}-acrylamide (59)

[0190] A mixture of nitro-compound 58 (127 mg, 0.27 mmol), SnCl₂ (429 mg, 2.26 mmol, 8.4 equiv.) and NH₄OAc (445 mg) was suspended in methanol (9.5 mL) and water (1.5 mL), and the mixture was heated at 70°C for 45 min. The mixture was diluted with ethylacetate (100 mL) and washed with brine and then saturated NaHCO₃, dried (MgSO₄), filtered, and concentrated. Purification by chromatographic column on silica gel (elution 5 to 10% methanol in dichloromethane) gave 52 mg (43% yield) of 59. ¹H-NMR (CDCl₃), δ (ppm): 8.25 (bs, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, J = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H).

Example 46

N-(2-aminophenyl)-3-(4-{[(3,4,5-trimethoxy-benzyl)-amino]-methyl}-phenyl)-acrylamide (compound 61)

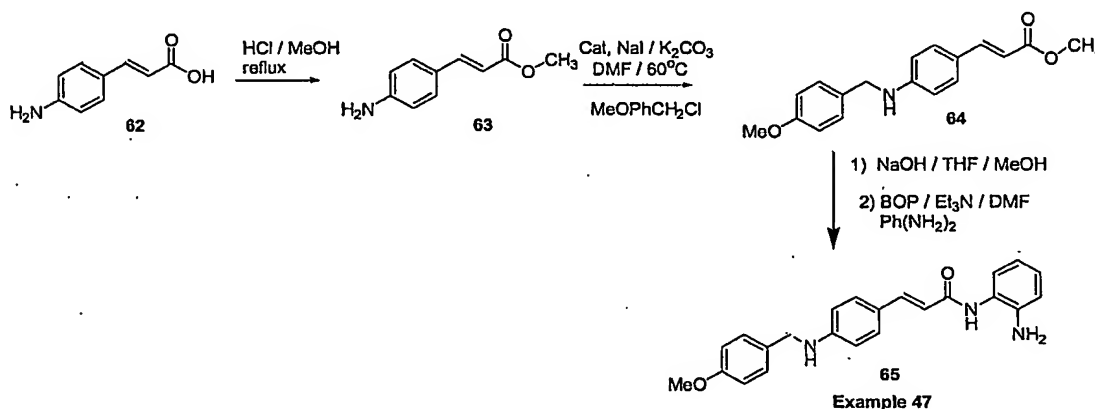
Step 1: 3-{4-{[Methyl-(3,4,5-trimethoxy-benzyl)-amino]-methyl}-phenyl}-N-(2-nitro-phenyl)-acrylamide (compound 60)

[0191] Amine 58 (180.2 mg, 0.38 mmol) was dissolved in 88% of HCO₂H (6 mL), treated with excess of paraformaldehyde (7.67 mmol) and the mixture stirred at 70°C for 2.5h. A saturated NaHCO₃ solution, was added slowly, extracted with dichloromethane (2 x 75 mL), dried (MgSO₄), filtered and concentrated. After chromatographic column on silica gel (elution 3 to 5% methanol in dichloromethane), pure N-methyl amine 60 (118 mg, 63% yield) was obtained. ¹³C NMR (300 MHz,

CDCl₃) δ (ppm): 164.5, 153.1, 143.5, 142.3, 136.8, 136.1, 136.0, 135.3, 134.9, 132.9, 129.3, 128.2, 125.8, 123.1, 122.2, 120.3, 105.4, 62.2, 61.2, 60.8, 56.0, 42.5. LRMS = 492.5 (M+1).

Step 2: N-(2-aminophenyl)-3-(4-[(3,4,5-trimethoxy-benzyl)-amino]-methyl)-phenyl)-acrylamide (compound 61)

[0192] Following the procedure described in Example 45, step 3, but substituting the nitro-compound 60 for 58, the title compound 61 was obtained in 72% yield. ¹H-NMR (DMSO-d₆), δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, J = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H).



Example 47

N-(2-aminophenyl)-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylamide (compound 65)

Step 1: Methyl-3-(4-amino-phenyl)-acrylate hydrochloride (compound 63)

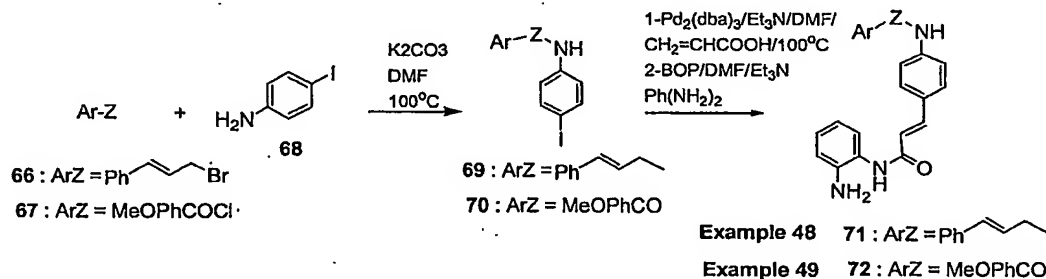
[0193] 4-amino-cinnamic acid (10.41 g, 0.052 mol) was dissolved in methanol (100 mL) at rt. A solution of HCl in dioxane (15.6 mL, 4 N) was then added. The reaction mixture was heated at reflux overnight. The clear solution was evaporated to a half volume and then settled down at rt. The white suspension obtained was collected by vacuum filtration. The mother liquid was evaporated again to a quart volume and cooled down to rt. The suspension was filtered again. The combined the solid collected from two filtration was dried *in vacuo* to give 7.16 g of 63 (64.3% yield). LRMS: 178 (M+1).

Step 2: Methyl-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylate hydrochloride (compound 64)

[0194] To a suspension of compound 63 (3.57 g, 16.7 mmol) in DMF (30 mL) was added Et₃N. after 10 min 4-methoxybenzyl chloride (2.0 g, 12.8 mmol), NaI (0.38 g, 2.6 mmol) and K₂CO₃ (3.53 g, 25.5 mmol) were added successively. The mixture was heated at 60°C overnight and evaporated to dryness. The residue was partitioned between NaHCO₃ sat. solution (50 mL) and EtOAc (50mLx3). The combined organic layers were washed with brine and then evaporated to dryness. The residue was purified by flash chromatography and then recrystallized from isopropylalcohol to give 1.16 g 64 (yield 30.6%, LRMS = 298) and 1.46g of 63 (49% recovered yield).

Step 3: N-(2-aminophenyl)-3-{4-(4-methoxy-benzylamino)-phenyl}-acrylamide (compound 65)

[0195] Following the procedure described in Example 42, step 4, but substituting 64 for 48, the title compound 65 was obtained in 32% yield. ¹H NMR: (DMSO-d₆) δ (ppm): 9.15 (s, 1H), 7.24-7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H).



Example 48

N-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (compound 71)

Step 1: N-(4-Iodo-phenyl)-(3-phenyl-allyl)-amine (compound 69)

[0196] Following the procedure described in Example 47, step 2, but substituting 68 for 63, the title compound 69 was obtained in 70% yield. LRMS = 288 (M+1)

Step 2: N-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)-acrylamide (71)

[0197] Following the procedure described in Example 42, steps 2, 4, but substituting 69 for 42, and acrylic acid for tert-butyl acrylate the title compound 71 was obtained in an overall yield of 60%. ¹H NMR:

(DMSO- d_6) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H).

Example 49

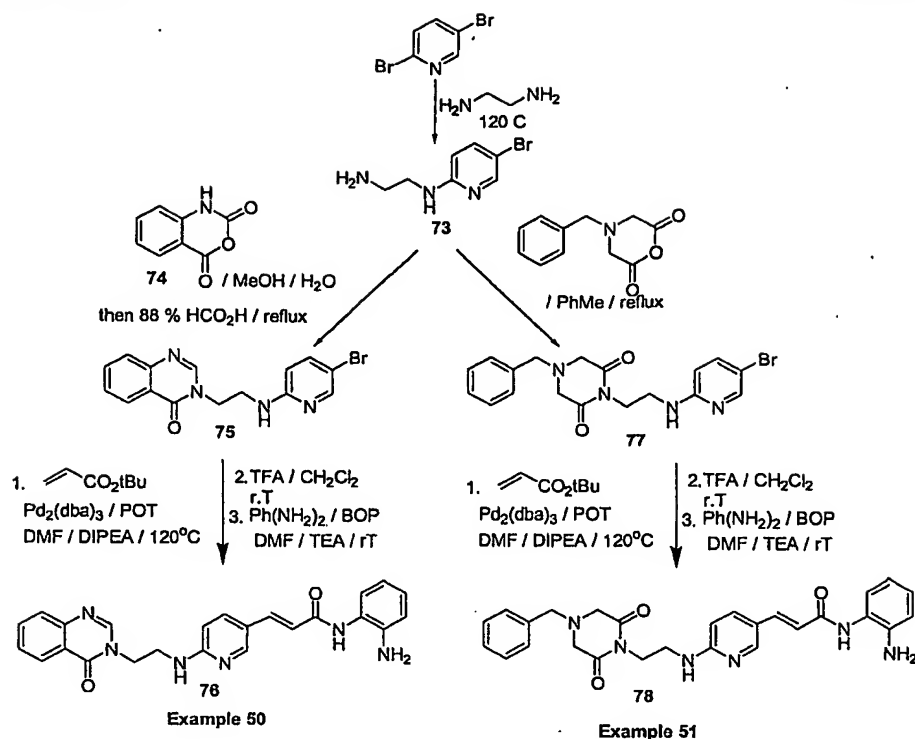
N-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)

Step 1: *N*-(4-Iodo-phenyl)-4-methoxy-benzamide (compound 70)

[0198] Following the procedure described in Example 47, step 2, but substituting 68 for 63, the title compound 70 was obtained in 90% yield. LRMS = 354.0 (M+1)

Step 2: *N*-(2-Amino-phenyl)-3-[4-(4-methoxy-benzamide)]-acrylamide (compound 72)

[0199] Following the procedure described in Example 42, steps 2, 4, but substituting 70 for 42, and acrylic acid for tert-butyl acrylate the title compound 72 was obtained in an overall yield of 90%. ^1H NMR: (DMSO- d_6) δ (ppm): 9.4 (bs, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H).



Example 50

N-(2-aminophenyl)-3-{6-[2-(4-oxo-4*H*-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 76)

Step 1: *N*-(5-Bromo-pyridin-2-yl)-ethane-1,2-diamine (compound 73)

[0200] Following the procedure described in Example 40, step 1, but using 1,2-diaminoethane as alkyl amine, the title compound 73 was obtained in 84% yield. ¹³C NMR (300 MHz, CD₃OD): 159.1, 148.7, 140.7, 111.7, 107.2, 44.3, 41.7. LRMS = 218.1 (M+1)

Step 2: 3-[2-(5-Bromo-pyridin-2-ylamino)-ethyl]-3*H*-quinazolin-4-one (compound 75)

[0201] A suspension of primary amine 73 (1.17 g, 5.40 mmol) and isatoic anhydride 74 (880 mg, 5.40 mmol) in methanol (25 mL) was stirred for 3 h at 50°C and then concentrated. The resulting oily residue was dissolved in 88% formic acid (20 mL) and refluxed overnight. After removal of formic acid, the solid residue was purified through column chromatography on silica gel (5% methanol in dichloromethane) to give 1.24 g (3.6 mmol, 67% yield) of 75. ¹³C NMR (300 MHz, CDCl₃): 161.6, 156.8, 147.7, 147.6, 147.2, 139.8, 134.5, 127.4, 126.8, 126.3, 121.6, 110.1, 107.0, 46.3, 40.1. LRMS = 347.1 (M+1).

Step 3: N-(2-aminophenyl)-3-{6-[2-(4-oxo-4H-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 76)

[0202] Following the procedure described in Example 42, steps 2 to 4, but substituting 75 for 42, the title compound 76 was obtained in an overall yield of 68 %. ¹H-NMR (DMSO-d₆), δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H).

Example 51

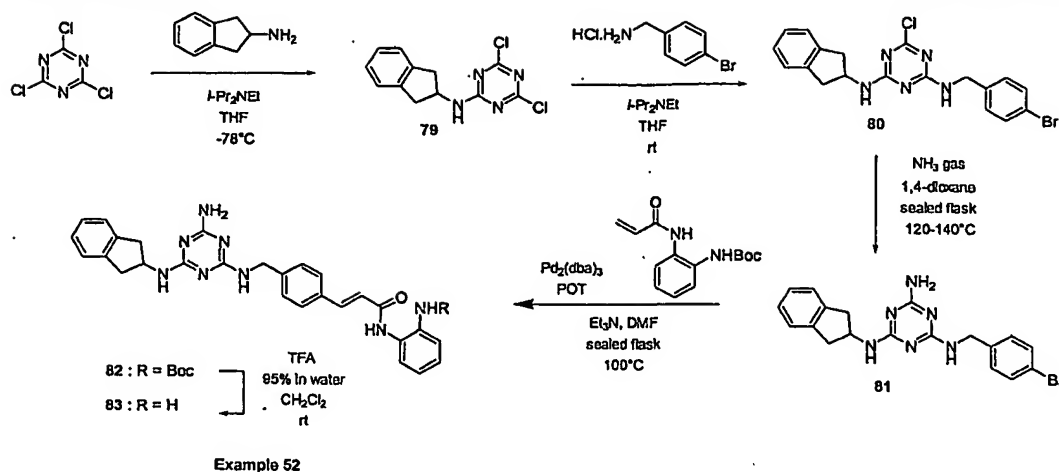
N-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 78)

Step 2: 4-Benzyl-1-[2-(5-bromo-pyridin-2-ylamino)-ethyl]-piperazine-2,6-dione (compound 77)

[0203] A suspension of benzyliminodiacetic acid (702 mg, 3.15 mmol) and acetic anhydride (15 mL) was stirred at 120°C for 45 min. The reaction mixture was diluted with dry toluene and concentrated in vacuo to remove the volatiles. The residue was dissolved in dry toluene (15 mL) and transferred via cannula to a reaction flask containing the amine 73 (475 mg, 3.2 mmol). The mixture was heated at 90°C for 16 h, concentrated and chromatographed by column on silica gel (elution 5% methanol in dichloromethane) to give 684mg (1.70 mmol, 54% yield) of 77.

Step 3: N-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide (compound 78)

[0204] Following the procedure described in Example 42, steps 2 to 4, but substituting 77 for 42, the title compound 78 was obtained in an overall yield of 60%. ¹H-NMR (CD₃OD-d₄), δ (ppm): 8.09 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.38 (s, 4H).



Example 52

(*E*)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-*N*-(2-amino-phenyl)-cinnamide (compound 83)

Step 1: 4,6-Dichloro-2-(2-indanyl-amino)-[1,3,5]triazine (compound 79)

[0205] To a stirred solution at -78°C of cyanuric chloride (13.15 g, 71.33 mmol) in anhydrous THF (100 mL) under nitrogen was slowly cannulated a solution of 2-aminoindan (10.00 g, 75.08 mmol), $i\text{-Pr}_2\text{NEt}$ (14.39 mL, 82.59 mmol) in anhydrous THF (60 mL). After 50 min, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ CH_2Cl_2 : 2/98 \rightarrow 5/95) and by co-precipitation (AcOEt/hexanes) to afford the title compound 79 (18.51 g, 65.78 mmol, 92% yield) as a beige powder. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.29-7.18 (m, 4H), 6.02 (bd, $J = 6.3$ Hz, 1H), 4.94-4.84 (m, 1H), 3.41 (dd, $J = 16.2, 6.9$ Hz, 2H), 2.89 (dd, $J = 16.1, 4.5$ Hz, 2H).

Step 2: 2-(4-Bromo-benzyl-amino)-4-chloro-6-(2-indanyl-amino)-[1,3,5]triazine (compound 80)

[0206] To a stirred solution at room temperature of 79 (2.68 g, 9.52 mmol) in anhydrous THF (50 mL) under nitrogen were added $i\text{-Pr}_2\text{NEt}$ (4.79 mL, 27.53 mmol) and 4-bromobenzylamine.HCl (2.45 g, 11.01 mmol), respectively. After 17 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After

separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{AcOEt}/\text{CH}_2\text{Cl}_2$: 3/97→5/95) to afford the title compound 80 (4.00 g, 9.29 mmol, 97% yield) as a white powder. ^1H NMR (300 MHz, CDCl_3) δ (ppm): mixture of rotamers, 7.52-7.42 (m, 2H), 7.26-7.11 (m, 6H), 6.51 and 6.12 (2 m, 1H), 5.72-5.46 (m, 1H), 4.94-4.64 (m, 1H), 4.62-4.46 (m, 2H), 3.43-3.16 (m, 2H), 2.92-2.74 (m, 2H).

Step 3: 4-Amino-2-(4-bromo-benzyl-amino)-6-(2-indanyl-amino)-[1,3,5]triazine (compound 81)

[0207] In a 75 mL sealed flask, a solution of 80 (2.05 g, 4.76 mmol) in anhydrous 1,4-dioxane (60 mL) was stirred at room temperature, saturated with NH_3 gas for 5 min, and warmed to 140°C for 18 h. The reaction mixture was allowed to cool to room temperature, the saturation step with NH_3 gas was repeated for 5 min, and the reaction mixture was warmed to 140°C again for 24 h. Then, the reaction mixture was allowed to cool to room temperature, poured into 1N HCl , and diluted with AcOEt . After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$: 5/95) to afford the title compound 81 (1.96 g, 4.76 mmol, quantitative yield) as a colorless foam. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.43 (d, $J = 8.2$ Hz, 2H), 7.25-7.12 (m, 6H), 5.70-5.10 (m, 2H), 5.00-4.65 (m, 3H), 4.52 (bs, 2H), 3.40-3.10 (m, 2H), 2.90-2.65 (m, 2H).

Step 4: (E)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-N-[2-(N-t-butoxycarbonyl)-amino-phenyl]-cinamide (compound 82)

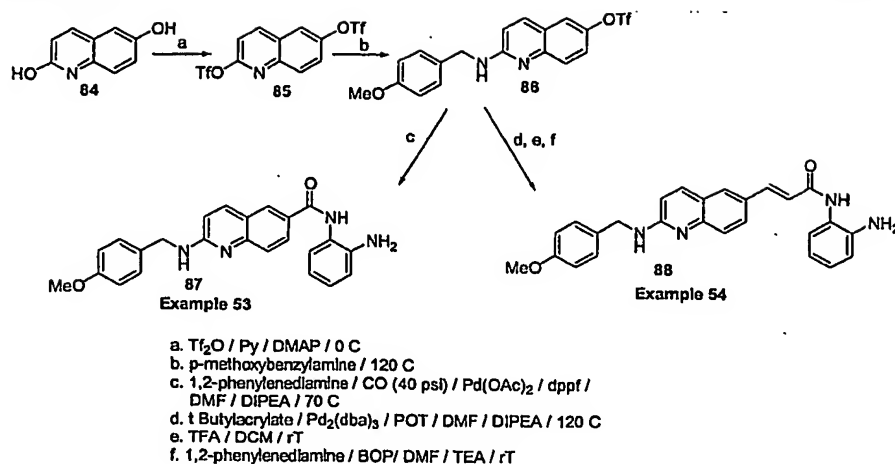
Preparation of N-[2-(N-t-Butoxycarbonyl)-amino-phenyl]-acrylamide

[0208] Following the procedure described in Example 45, step 2, but substituting the nitro-compound 2-(N-t-butoxycarbonyl)-amino-aniline for 2-nitroaniline, the title compound was obtained in 77% yield. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.51 (bs, 1H), 7.60-7.45 (m, 1H), 7.38-7.28 (m, 1H), 7.20-7.05 (m, 2H), 6.98 (bs, 1H), 6.41 (dd, $J = 17.0$ Hz, 1.1 Hz, 1H), 6.25 (dd, $J = 16.9$ Hz, 10.0 Hz, 1H), 5.76 (dd, $J = 10.2$ Hz, 1.4 Hz, 1H), 1.52 (s, 9H).

[0209] In a 50 mL sealed flask, a solution of **81** (300 mg, 0.73 mmol), the acrylamide (230 mg, 0.88 mmol), Et₃N (407 μ l, 2.92 mmol), tri-*o*-tolylphosphine (POT, 13 mg, 0.04 mmol), Pd₂(dba)₃ (20 mg, 0.02 mmol) in anhydrous DMF (10 mL) was stirred at room temperature, saturated with N₂ gas for 15 min, and warmed to 100°C for 15 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 2/98→5/95) to afford the title compound **82** (240 mg, 0.41 mmol, 56% yield) as a beige solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.46 (bs, 1H), 7.71 (bd, J = 15.7 Hz, 1H), 7.62-7.05 (m, 13H), 6.54 (bd, J = 15.9 Hz, 1H), 5.95-4.90 (m, 4H), 4.85-4.48 (m, 3H), 3.40-3.14 (m, 2H), 2.90-2.70 (m, 2H), 1.52 (s, 9H).

Step 5: (E)-4-{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl-amino]-methyl}-N-(2-amino-phenyl)-cinnamide (compound 83)

[0210] To a stirred solution at room temperature of **82** (230 mg, 0.39 mmol) in CH₂Cl₂ (5 mL) was added TFA (1 mL, 95% in water). After 18 h, the reaction mixture was poured into a saturated aqueous solution of NaHCO₃, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NaHCO₃, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 5/95) to afford the title compound **83** (170 mg, 0.35 mmol, 89% yield) as a yellow solid. ¹H NMR (300 MHz, acetone-d₆) δ (ppm): 8.87 (bs, 1H), 7.69 (d, J = 15.7 Hz, 1H), 7.59 (bd, J = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H).



Example 53

N-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound 87)

Step 1: 2,6-ditrifluoromethanesulfonyloxy-quinoline (compound 85):

[0211] A solution of 2,6-dihydroxyquinoline **84** (1.254 g, 7.78 mmol) and DMAP (a few crystals) in dry pyridine (15 mL) was treated with neat trifluoromethanesulfonyl anhydride (5.2 g, 18.4 mmol, 1.2 equiv.) and stirred at 0°C for 5 h. This solution was then poured on a mixture brine/sat NaHCO₃ and extracted with dichloromethane (2 x 150 mL), dried (MgSO₄), filtered and concentrated. Purification by column chromatography on silica gel (30% to 50% ether in hexanes) gave 2.58 g (6.1 mmol, 78% yield) of **85**. ¹³C NMR (300 MHz, CDCl₃): 154.5, 147.8, 144.6, 142.0, 131.6, 127.8, 124.9, 119.3, 118.7, 114.9. LRMS = 426.0 (M+1).

Step 2: N-(2-aminophenyl)-2-(4-methoxy-benzylamino)-quinolin-6-yl-amide (compound 87)

[0212] Following the procedure described in Example 40, steps 1, 2, but substituting **85** for **40**, the title compound **87** was obtained in 92% yield. ¹H-NMR (DMSO-d₆), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H).

Example 54

N-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)

Step 3: *N*-(2-aminophenyl)-3-[2-(4-methoxy-benzylamino)-quinolin-6-yl]-acrylamide (compound 88)

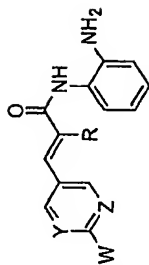
[0213] Following the procedure described in Example 42, steps 1 to 4, but substituting 85 for 40, the title compound 88 was obtained in an overall yield of 71%. ¹H-NMR (DMSO-*d*₆), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H).

Examples 55-84

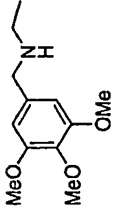
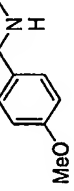
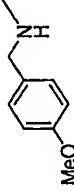
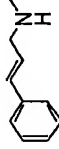
[0214] Examples 55 to 84 describe the preparation of compounds 89 to 118 using the same procedures as described for compounds 44 to 88 in Examples 40 to 54. Characterization data are presented in Tables 3a-d.

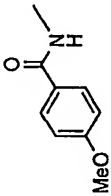
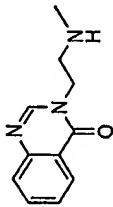
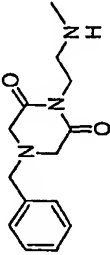
Table 3a.

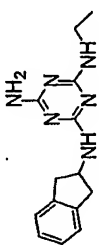
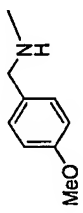
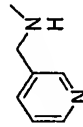
Characterization of Compounds Prepared in Examples 42-84


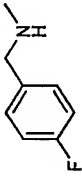
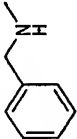


| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|---|----|----|---|---|---|------|
| 42 | 50 | | N | CH | H | N-(2-aminophenyl)-3-[(2-phenylamino)ethylamino]pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.25 (bs, 1H), 8.21 (d, J = 1.6 Hz, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.24 (t, J = 1.0 Hz, 1H), 7.08 (t, J = 7.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 1H), 6.75 (dt, J = 8.0 Hz, 0.4 Hz, 1H), 6.57 (m, 6H), 5.20 (bs, 1H), 3.48 (t, J = 6.3 Hz, 2H), 3.33 (bs, 2H), 3.21 (t, J = 6.3 Hz, 2H) | 3 |
| 44 | 55b | | CH | CH | H | {4-[2-(2-amino-phenyl)carbamoyl]-vinyl}-phenyl}-carbamamic acid pyridin-3-yl methyl ester | ¹ H NMR: (DMSO-d ₆) δ (ppm): 10.03 (s, 1H), 9.32 (s, 1H), 8.65 (s, 1H), 8.55 (d, J = 3.3 Hz, 1H), 7.85 (d, J = 7.69 Hz, 1H), 7.40-7.60 (m, 6H), 7.31 (d, J = 7.69 Hz, 1H), 6.89 (dd, J = 7.14 Hz, J = 7 Hz, 1H), 6.71-6.79 (m, 2H), 6.55 (dd, J = 7.1 Hz, J = 7 Hz, 1H), 5.20 (s, 2H), 4.93 (bs, 2H) | 4 |


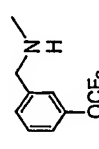
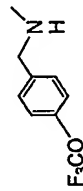
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|---|----|----|----|---|--|------|
| 45 | 59 |  | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxybenzylamino)methyl]phenyl}acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 8.25 (bs, 1H), 7.59 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 7.25 (m 1H), 7.02 (t, J = 6.8 Hz, 1H), 6.75 (m, 2H), 6.62 (d, J = 15.6 Hz, 1H), 6.58 (s, 2H), 3.97 (bs, 3H), 3.80 (s, 9H), 3.78 (s, 2H), 3.72 (s, 2H). | 5 |
| 46 | 61b |  | N | CH | Me | N-(2-aminophenyl)-3-[6-(4-methoxybenzylamino)pyridin-3-yl]-2-methylacrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.15 (bs, 1H), 8.13 (bs, 1H), 7.58 (d, J = 1.9 Hz, 1H), 7.30 (m 4H), 7.12 (d, J = 7.7 Hz, 1H), 6.91 (m 3H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (m 2H), 4.83 (bs, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H), 3.33 (s, 3H). | 3 |
| 47 | 65 |  | CH | CH | H | N-(2-amino-phenyl)-3-[4-(4-methoxybenzylamino)phenyl]acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.15 (s, 1H), 7.24 -7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H). | 6 |
| 48 | 71 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-styrylamino-phenyl)acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.22 (bs, 1H), 7.45 (d, J = 6.9 Hz, 2H), 7.39 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 7.26 (dt, J = 7.4 Hz, 6.8 Hz, 2H), 6.93 (dt, J = 7.9 Hz, 7.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.5 Hz, 2H), 6.63-6.55 (m, 4H), 6.44-6.37 (m, 1H), 4.95 (bs, 2H), 3.95 (bs, 2H). | 7 |

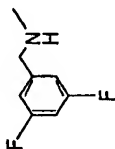
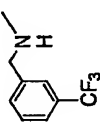
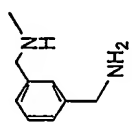
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|----|----|---|--|--|------|
| 49 | 72 |  | CH | CH | H | N-{4-[2-(2-Amino-phenylcarbamoyl)-vinyl]-phenyl}-4-methoxybenzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.4 (bs, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H). | 7 |
| 50 | 76 |  | N | CH | H | N-(2-aminophenyl)-3-{6-[2-(4-oxo-4H-quinazolin-3-yl)-ethylamino]-pyridin-3-yl}-acrylamide | ¹ H-NMR (DMSO-d ₆) δ (ppm): 9.24 (bs, 1H), 8.17 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 8.11 (bs, 1H), 8.08 (d, J = 1.9 Hz, 1H), 7.82 (dt, J = 8.5 Hz, 1.4 Hz, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.25 (t, J = 5.8 Hz, 1H), 6.90 (dt, J = 15.7 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.58 (m, 3H), 4.95 (bs, 2H), 4.17 (t, J = 5.2 Hz, 2H), 3.68 (m, J = 5.2 Hz, 2H). | 8 |
| 51 | 78 |  | N | CH | H | N-(2-aminophenyl)-3-{6-[2-(4-benzyl-2,6-dioxo-1-piperazin-1-yl)-ethylamino]-pyridin-3-yl}-acrylamide | ¹ H-NMR (CD ₃ OD-d ₄) δ (ppm): 8.09 (d, J = 1.8 Hz, 1H), 7.68 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.53 (d, J = 15.6 Hz, 1H), 7.29 (m, 6H), 7.20 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.02 (dt, J = 9.0 Hz, 1.2 Hz, 1H), 6.86 (dd, J = 8.1 Hz, 1.2 Hz, 1H), 6.73 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 6.61 (d, J = 15.6 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 4.85 (bs, 3H), 3.97 (t, J = 7.5 Hz, 2H), 3.60 (s, 2H), 3.57 (t, J = 7.5 Hz, 2H), 3.38 (s, 4H). | 8 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|----|----|---|---|--|------|
| 52 | 83 |  | CH | CH | H | (E)-4-{{[4-Amino-6-(2-indanyl-amino)-[1,3,5]triazin-2-ylamino]-N-(2-methyl)-N-(2-amino-phenyl)-cinamide | ¹ H-NMR (300 MHz, acetone-d ₆) δ (ppm): 8.87 (bs, 1H), 7.69 (d, J = 15.7 Hz, 1H), 7.59 (bd, J = 7.7 Hz, 2H), 7.49-7.34 (m, 3H), 7.28-7.11 (m, 4H), 7.05-6.91 (m, 2H), 6.88 (dd, J = 8.0, 1.4 Hz, 1H), 6.69 (td, J = 7.6, 1.4 Hz, 1H), 6.65-5.50 (m, 4H), 4.83-4.53 (m, 5H), 3.34-3.11 (m, 2H), 2.98-2.80 (m, 2H). | 9 |
| 55 | 89 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(4-methoxybenzylamino)-pyridin-3-yl]-acrylamide | ¹ H-NMR (DMSO-d ₆) δ (ppm): 9.24 (bs, 1H), 8.19 (d, J = 1.6 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 5.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 6.90 (m, 1H), 6.88 (dd, J = 8.5 Hz, 2H), 6.74 (d, J = 6.9 Hz, 1H), 6.58 (m, 3H), 4.92 (bs, 2H), 4.45 (d, J = 5.5 Hz, 2H), 3.72 (s, 3H). | 3 |
| 56 | 90 |  | N | CH | H | N-(2-aminophenyl)-3-{6-[(pyridin-3-ylmethyl)-amino]-pyridin-3-yl}-acrylamide | ¹ H-NMR (CD ₃ OD-d ₄) δ (ppm): 8.47 (bs, 1H), 8.33 (bs, 1H), 8.02 (m, 1H), 7.73 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 15.4 Hz, 1H), 7.29 (m, 1H), 7.14 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.66 (t, J = 7.9 Hz, 1H), 6.53 (m, 2H), 4.54 (m, 2H), 3.59 (bs, 2H). | 3 |

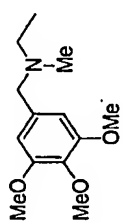
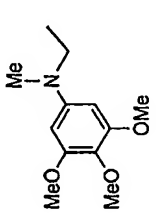
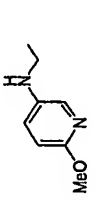
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|---|---|----|---|--|--|------|
| 57 | 91 |  | N | CH | H | N-(2-aminophenyl)-3-[(pyridin-4-ylmethyl)amino]pyridin-3-yl}acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.27 (bs, 1H), 8.48 (dd, J = 1.6 Hz, 4.4, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.70 (m, 2H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (m, 3H), 6.90 (t, J = 6.9 Hz, 1H), 6.73 (d, J = 6.9 Hz, 1H), 6.58 (m, 4H), 4.98 (bs, 2H), 4.57 (d, J = 6.0 Hz, 2H). | 3 |
| 58 | 92 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(4-fluorobenzylamino)pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.24 (bs, 1H), 8.18 (d, J = 1.6 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 0.8 Hz, 1H), 7.60 (t, J = 5.8 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.36 (m, 3H), 7.13 (t, J = 8.8 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.73 (dd, J = 6.9 Hz, 1.0 Hz, 1H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.50 (d, J = 6.0 Hz, 2H). | 3 |
| 59 | 93 |  | N | CH | H | N-(2-aminophenyl)-3-(6-benzylamino)pyridin-3-yl}acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.24 (bs, 1H), 8.17 (d, J = 1.9 Hz, 1H), 7.65 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 7.60 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.31 (m, 5H), 7.23 (m, 1H), 6.89 (dt, J = 8.0 Hz, 1.6 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 6.58 (m, 3H), 4.92 (bs, 2H), 4.53 (d, J = 6.0 Hz, 2H). | 3 |

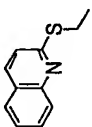
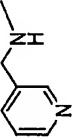

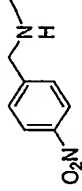
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|---|---|----|---|--|---|------|
| 60 | 94 | | N | CH | H | N-(2-aminophenyl)-3-[6-(3-phenylpropylamino)pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.22 (bs, 1H), 8.18 (ds, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 15.4 Hz, 1H), 7.22 (m 7H), 6.90 (t, J = 7.7 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (m 3H), 4.92 (bs, 2H), 3.29 (dt, J = 7.7 Hz, 6.0 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 1.84 (m, J = 7.7 Hz, 2H). | 3 |
| 61 | 95 | | N | CH | H | N-(2-aminophenyl)-3-[6-(4-methoxyphenyl)ethylamino]pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.13 (m, 1H), 6.91 (m, 1H), 6.85 (d, J = 7.9 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.57 (m 3H), 4.92 (bs, 2H), 3.71 (s, 3H), 3.47 (dd, J = 7.3 Hz, 6.0 Hz, 2H), 2.78 (t, J = 7.3 Hz, 2H). | 3 |
| 62 | 96 | | N | CH | H | N-(2-aminophenyl)-3-[6-(4-dimethylaminobenzylamino)pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.23 (bs, 1H), 8.18 (bs, 1H), 7.63 (d, J = 8.2 Hz, 1H), 7.41 (m 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.0 Hz, 1H), 6.68 (d, J = 8.5 Hz, 2H), 6.58 (m, 3H), 4.91 (bs, 2H), 4.39 (d, J = 5.5 Hz, 2H), (bs, 2H). | 3 |

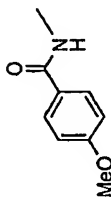
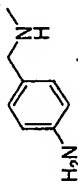
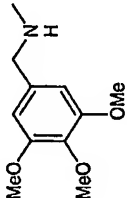
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|---|----|---|---|--|------|
| 63 | 97 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(3-imidazol-1-yl-propylamino)-pyridin-3-yl]-acrylamide | ¹ H-NMR (CD ₃ OD-d ₄), δ (ppm): 8.09 (bs, 1H), 8.05 (d, J = 1.9 Hz, 1H), 7.67 (m, 2H), 7.49 (d, J = 15.7 Hz, 1H), 7.28 (m, 2H), 7.17 (m, 2H), 6.98 (dt, J = 13.7 Hz, 7.7 Hz, 1H), 6.83 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.69 (dt, J = 9.1 Hz, 1.4 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.29 (m, 2H), 2.08 (m, J = 6.9 Hz, 2H). | 3 |
| 64 | 98 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(3-trifluoromethoxy-xy-benzylamino)-pyridin-3-yl]-acrylamide | ¹ H-NMR (acetone-d ₆), δ (ppm): 8.75 (bs, 1H), 8.23 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 15.4 Hz, 1H), 7.43 (m, 2H), 7.34 (bs, 2H), 7.19 (d, J = 6.6 Hz, 1H), 6.93 (m, 2H), 6.83 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (m, 3H), 4.71 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H). | 3 |
| 65 | 99 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(4-trifluoromethoxy-xy-benzylamino)-pyridin-3-yl]-acrylamide | ¹ H-NMR (acetone-d ₆), δ (ppm): 8.81 (bs, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.66 (d, J = 7.4 Hz, 1H), 7.56 (d, J = 15.7 Hz, 2H), 7.49 (d, 2H), J = 8.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 6.93 (m, 2H), 6.73 (m, 3H), 4.67 (d, J = 6.0 Hz, 2H), 4.66 (bs, 2H). | 3 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|---|----|---|---|---|------|
| 66 | 100 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(3,5-difluorobenzylamino)pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.25 (bs, 1H), 8.18 (d, J = 2.2 Hz, 1H), 7.67 (m, 2H), 7.42 (d, J = 15.7 Hz, 1H), 7.31 (d, J = 7.7 Hz, 1H), 7.08 (dt, J = 9.3 Hz, 2.2 Hz, 1H), 7.03 (dd, J = 8.8 Hz, 1.9 Hz, 2H), 6.90 (dt, J = 7.3 Hz, 1.4 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.92 (bs, 2H), 4.56 (d, J = 6.0 Hz, 2H). | 3 |
| 67 | 101 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(3-trifluoromethyl-1-benzylamino)pyridin-3-yl]acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.25 (bs, 1H), 8.14 (bs, 1H), 7.86 (m, 6H), 7.42 (d, J = 15.6 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 6.90 (dt, J = 8.8 Hz, 1.1 Hz, 1H), 6.74 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.60 (m 3H), 4.96 (bs, 2H), 4.63 (d, J = 5.8 Hz, 2H). | 3 |
| 68 | 102 |  | N | CH | H | 3-[6-(3-aminomethyl-1-benzylamino)pyridin-3-yl]N-(2-aminophenyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.28 (bs, 1H), 8.17 (bs, 1H), 7.66 (d, J = 5.8 Hz, 2H), 7.37 (m, 6H), 6.88 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.73 (dd, J = 8.0 Hz, 0.9 Hz, 1H), 6.59 (m 3H), 4.55 (d, J = 5.8 Hz, 2H), 3.96 (s, 2H), 3.37 (bs, 4H). | 3 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|---|----|----|---|---|--|------|
| 70 | 104 | | CH | CH | H | {4-[2-(2-amino-phenylcarbamoyl)-1)-vinyl]-benzyl}-carbamic acid pyridin-3-yl methyl ester | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.36 (s, 1H), 8.57 (s, 1H), 8.51 (d, J = 4.6 Hz, 1H), 7.91 (m, 1H), 7.77 (d, J = 7.68 Hz, 1H), 7.28-7.57 (m, 7H), 6.88 (dd, J = 15.66 Hz, 4.4 0 Hz, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.01 (s, 2H), 4.93 (bs, 2H), 4.10 (d, J = 6.04 Hz, 2H). | 4 |
| 71 | 105 | | CH | CH | H | (2-{4-[2-(2-amino-phenylcarbamoyl)-1)-vinyl]-phenyl}-ethyl)-carbamic acid pyridin-3-yl methyl ester | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.34 (s, 1H), 8.52 (m, 2H), 7.71 (d, J = 7.69 Hz, 1H), 7.20-7.60 (m, 8H), 6.87 (m, 2H), 6.73 (m, 1H), 6.56 (m, 1H), 5.03 (s, 2H), 4.92 (s, 2H), 3.30 (m, 2H), 2.75 (m, 2H). | 4 |
| 72 | 106 | | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxyphenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (acetone-d ₆), δ (ppm): 8.49 (bs, 1H), 8.41 (d, J = 7 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8 Hz, 2H), 7.45 (d, J = 8 Hz, 2H), 7.07 (m, 2H), 6.90 (d, J = 15.6 Hz, 1H), 6.76 (m, 1H), 6.74 (m, 1H), 5.99 (s, 2H), 4.36 (s, 2H), 3.69 (s, 6H), 3.68 (bs, 2H), 3.67 (s, 3H). | 5 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|----|----|---|--|---|------|
| 73 | 107 |  | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxybenzyl)-amino]-methyl}-phenyl}-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 7.70 (bs, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.33 (d, J = 4.9 Hz, 2H), 7.26 (d, J = 4.9 Hz, 2H), 7.25 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.75 (m, 1H), 6.61 (s, 2H), 6.57 (m, 1H), 4.08 (bs, 2H), 3.86 (s, 6H), 3.83 (s, 3H), 3.50 (s, 2H), 3.47 (s, 2H), 2.21 (s, 3H). | 5 |
| 74 | 108 |  | CH | CH | H | N-(2-aminophenyl)-3-{4-[(3,4,5-trimethoxyphenyl)-amino]-methyl}-phenyl}-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 7.74 (d, J = 15.4 Hz, 1H), 7.50 (d, J = 7.4 Hz, 2H), 7.25 (m, 3H), 7.06 (t, J = 1.9 Hz, 1H), 6.82 (d, J = 7.4 Hz, 2H), 6.58 (d, J = 15.4 Hz, 1H), 5.96 (s, 2H), 4.50 (s, 2H), 3.79 (s, 6H), 3.78 (bs, 2H), 3.77 (s, 3H), 3.00 (s, 3H). | 5 |
| 75 | 109 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(6-methoxypyridin-3-ylamino)-methyl]-phenyl}-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.4 (bs, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.54-7.45 (m, 3H), 7.87 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.95-6.77 (m, 3H), 6.62 (d, J = 7.7 Hz, 2H), 6.08-6.04 (m, 2H), 4.98 (bs, 2H), 3.72 (s, 3H). | 5 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|----|----|---|--|---|------|
| 76 | 110 |  | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(quinolin-2-ylsulfanylmethyl)-phenyl]-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.41 (bs, 1H), 8.21 (d, J = 8.5, 1H), 7.97 (dt, J = 7.7, 8.8 Hz, 2H), 7.78 (dt, J = 7.1 Hz, 8.2 Hz, 1H), 7.61-7.53 (m, 5H), 7.40 (dd, J = 8.5 Hz, 7.6 Hz, 2H), 6.97-6.77 (m, 4H), 6.6 (dt, J = 7.7 Hz, 7.5 Hz, 1H), 4.98 (bs, 2H), 4.65 (bs, 2H). | 5 |
| 77 | 111 |  | CH | CH | H | N-(2-amino-phenyl)-3-[4-(pyridin-3-ylmethyl)-amino]-phenyl-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.15 (s, 1H), 7.24-7.38 (m, 6H), 6.84-6.90 (m, 3H), 6.72 (m, 2H), 6.49-6.60 (m, 4H), 4.84 (s, 2H), 4.22 (d, J = 5.77 Hz, 2H). | 6 |
| 78 | 112 |  | N | CH | H | N-(2-Amino-phenyl)-3-(6-styrylamino-pyridin-3-yl)-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 7.96 (d, J=9.1 Hz, 2H), 7.55 (d, J = 14.2 Hz, 1H), 7.48 (d, J = 7.4 Hz, 2H), 7.39-7.29 (m, 4H), 7.07-6.91 (m, 3H), 6.81-6.64 (m, 3H), 6.47-6.38 (m, 1H), 4.21 (bs, 2H). | 7 |
| 79 | 113 |  | N | N | H | N-(2-amino-phenyl)-3-[2-(4-nitro-benzylamino)-pyrimidin-5-yl]-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.30 (s, 1H), 8.58 (bs, 2H), 8.36 (m, 1H), 8.20 (m, 2H), 7.58 (m, 2H), 7.28-7.42 (m, 2H), 6.52-6.92 (m, 4H), 4.90 (s, 2H), 4.64 (d, J = 6 Hz, 2H). | 7 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|--|---|----|---|---|---|------|
| 80 | 114 |  | N | CH | H | N-(5-[2-(2-amino-phenyl)carbamoyl-1-vinyl]-pyridin-2-yl)-4-methoxybenzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 10.87 (bs, 1H), 9.45 (bs, 1H), 8.66 (bs, 1H), 8.33 (d, J = 7.4 Hz, 1H), 8.14-8.08 (m, 3H), 7.63 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 6.8 Hz, 2H), 6.97 (d, J = 12.3 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 5.06 (bs, 2H), 3.88 (s, 3H) | 7 |
| 81 | 115 |  | N | N | H | 3-[2-(4-amino-benzylamino)-pyrimidin-5-yl]-N-(2-amino-phenyl)-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.27 (s, 1H), 8.83 (s, 2H), 7.97 (t, J = 6 Hz, 1H), 7.37 (d, J = 15.9 Hz, 1H), 7.29 (d, J = 7.11 Hz, 1H), 6.96 (d, J = 8.24 Hz, 2H), 6.88 (m, 1H), 6.70 (m, 2H), 6.55 (m, 1H), 6.47 (d, J = 8.2 Hz, 2H), 4.90 (s, 4H), 4.34 (d, J = 6.0 Hz, 2H). | 7 |
| 82 | 116 |  | N | CH | H | N-(2-aminophenyl)-3-[6-(3,4,5-trimethoxybenzylamino)-pyridin-3-yl]-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 8.38 (bs, 1H), 7.49 (m, 1H), 7.42 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.41 (m, 1H), 7.30 (d, J = 7.9 Hz, 1H), 7.10 (bs, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 15.0 Hz, 1H), 6.73 (m, 1H), 6.65 (m, 2H), 6.36 (d, J = 8.8 Hz, 1H), 6.23 (d, J = 15.0 Hz, 1H), 4.34 (s, 2H and bs, 2H), 3.84 (s, 3H), 3.81 (s, 6H). | 7, 3 |

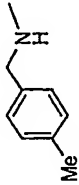
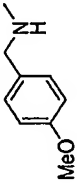
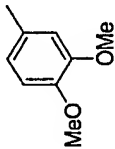
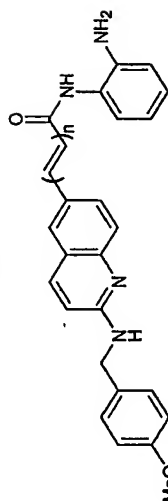
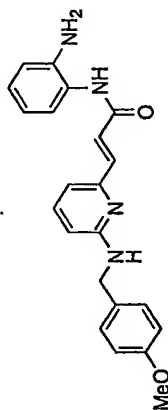
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|----------|---|---|----|---|--|---|----------|
| 83 | 117 |  | N | CH | H | N-(2-Amino-phenyl)-3-[6-(4-methylbenzylamino)-pyridin-3-yl]-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 8.28 (bs, 1H), 7.98 (d, J = 9.6 Hz, 1H), 7.57 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.29 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.6 Hz, 2H), 6.98 (dt, J = 8.2 Hz, 2H), 6.87 (t, J = 8.2 Hz, 1H), 6.75 (d, J = 15.1 Hz, 1H), 4.57 (s, 2H), 2.53 (s, 3H). | 7 |
| 84 | 118 |  | N | N | H | N-(2-amino-phenyl)-3-[2(4-methoxybenzylamino)-pyrimidin-5-yl]-acrylamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.27 (s, 1H), 8.54 (s, 2H), 8.12 (m, 1H), 7.30 (m, 4H), 6.53-6.91 (m, 6H), 4.90 (s, 2H), 4.46 (d, J = 4.9 Hz, 2H), 3.7 (s, 3H). | 7 |
| 84 b | 118 b |  | N | CH | H | N-(2-Amino-phenyl)-3-[6-(3,4-dimethoxyphenyl)-pyridin-3-yl]-acrylamide | ¹ H NMR (20% CD ₃ OD in CDCl ₃): 8.75 (s, 1H), 7.95 (m, 1H), 7.74-7.59 (m, 3H), 7.50 (m, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.07 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.89-6.83 (m, 3H), 3.96 (s, 3H), 3.91 (s, 3H). | 9, 15 |

Table 3b



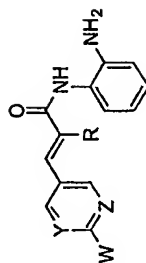
| Ex | Cpd | n | Name | Characterization | Scheme |
|----|-----|---|--|---|--------|
| 53 | 87 | 0 | 2-(4-methoxybenzylamino)-quinoline-6-carboxylic acid (2-aminophenyl)-amide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.66 (bs, 1H), 8.32 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (dd, J = 9.1 Hz, 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.34 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 7.20 (d, J = 7.7 Hz, 1H), 6.97 (t, J = 7.7 Hz, 1H), 6.90 (m 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 6.3 Hz, 1H), 4.90 (bs 2H), 4.58 (d, J = 3.3 Hz, 2H), 3.73 (s, 3H), 3.33 (bs, 1H). | 10 |
| 54 | 88 | 1 | N-(2-aminophenyl)-3-[2-(4-methoxybenzylamino)-quinolin-6-yl]-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.70 (bs, 1H), 9.40 (bs, 1H), 8.20 (d, J = 8.9 Hz, 1H), 8.03 (bs, 2H), 7.94 (d, J = 7.2 Hz, 1H), 7.64 (dd, J = 15.7 Hz, 2.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.39 (m, 1H), 7.14 (d, J = 8.9 Hz, 1H), 7.05 (d, J = 15.7 Hz, 1H), 6.97 (m, 1H), 6.95 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H), 3.75 (s, 3H). | 10 |

Table 3c



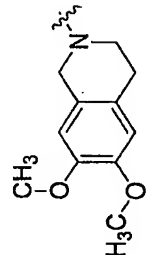
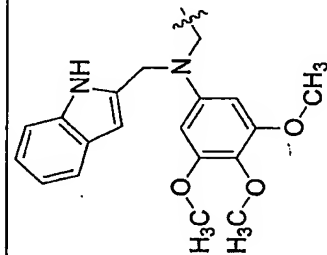
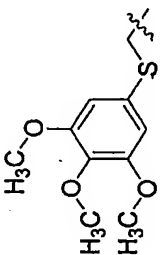
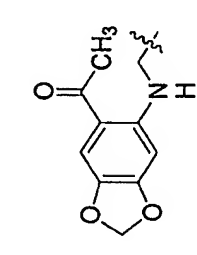
| Ex. | Cpd. | Name | Characterization | Scheme |
|-----|------|--|---|--------|
| 43 | 51 | N-(2-aminophenyl)-3-[(4-methoxybenzyl)pyridin-2-yl]-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 7.60 (bs, 1H), 7.55 (bs, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 15.1 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.88 (d, J = 8.3 Hz, 2H), 6.80 (m, 2H), 6.70 (m, 3H), 6.41 (d, J = 8.5 Hz, 1H), 4.50 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 3.45 (bs, 2H). | 3 |

Table 3d

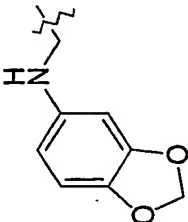
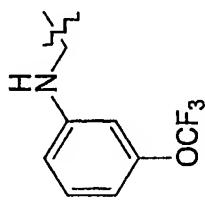
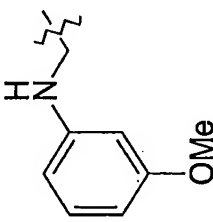
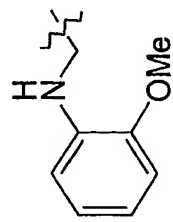


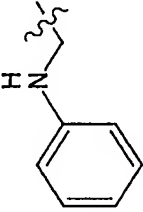
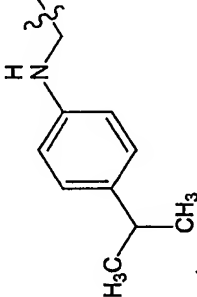
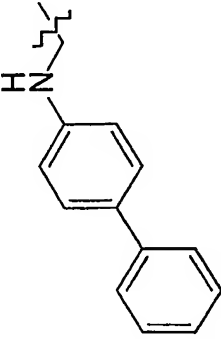
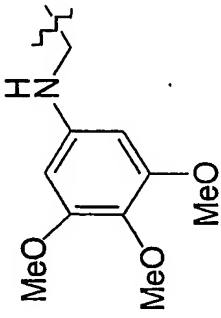
| Ex. | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|-----|-----|---|----|---|---|---|--|------|
| 347 | 492 | | CH | H | H | N-(2-Amino-phenyl)-3-{4-[(4,6-dimethoxy-pyrimidin-2-ylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.36 (bs, 1H), 7.55 (d, J = 7.4 Hz, 2H), 7.48 (s, 1H), 7.38 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 6.91 (m, 2H), 6.73 (d, J = 8.2 Hz, 1H), 6.56 (dd, J = 7.4, 7.7 Hz, 1H), 5.35 (s, 1H), 4.93 (bs, 2H), 4.46 (dd, J = 6.04 Hz, 2H), 3.32 (s, 6H) | 3, 7 |

| Ex. | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|--|------|
| 348 | 493 | | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(4-chloro-6-methoxypyrimidin-2-ylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆) , δ (ppm): 9.37 (bs, 1H), 7.58-7.50 (m, 3H), 7.37-7.32 (m, 3 H), 6.94-6.83 (m, 2H), 6.75 (d J=8.0 Hz, 1H), 6.57 (t, J=7.5, 1H), 6.13 (bs, 1H), 4.94 (bs, 2H), 4.48 (d, J=6.0, 2H), 3.84 (s, 3H) | 3, 7 |
| 349 | 494 | | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(3,5-dimethoxybenzylamino)-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆) , δ (ppm): 9.38 (bs, 1H), 7.55-7.40 (m, 6H), 6.88-6.57 (m, 3 H), 6.35-6.32 (m, 1H), 5.73 (m, 3H), 4.94 (s, 2 H), 4.26 (s, 2H), 3.63 (s, 6H). | 3, 7 |
| 350 | 495 | | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(3,5-dinitrobenzylamino)-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆) , δ (ppm): 9.38 (bs, 1H), 7.74 (bs, 3H), 7.61 (d, J=8.2 Hz, 2 H), 7.56-7.44 (m, 3H), 7.32 (d J=8.0 Hz, 1H), 6.91-6.85 (m, 2H), 6.73 (d, J=7.9 Hz, 1H), 6.66-6.56 (m, 1H), 4.93 (bs, 2H), 4.52 (bs, 2H). | 3, 7 |
| 351 | 496 | | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(3-trifluoromethoxybenzylamino)-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆) , δ (ppm): 9.22 (bs, 1H), 7.52 (d, J=7.9 Hz, 2H), 7.44 (bs, 1H), 7.38 (bs, 3H), 7.28 (d J=6.9 Hz, 2H), 6.95-6.92 (m, 2H), 6.79 (d, J=8.2 Hz, 1H), 6.69-6.59 (m, 3H), 4.95 (bs, 2H), 4.45 (bs, 2H). | 58 |
| 352 | 497 | | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxyphenoxy)methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆) , δ (ppm): 9.45 (bs, 1H); 8.01 (bs, 2H), 7.78-7.5 (m, 4H), 7.49-7.40 (m, 1H), 6.98 (dd, J=7.0, 8.2 Hz, 1H), 6.82 (d, J=7.0 Hz, 1H), 6.64 (dd, J=7.0, 7.6 Hz, 1H), 6.41 (bs, 2H), 5.17 (s, 2H), 3.81 (s, 6H), 3.64 (s, 3H). | 3, 7 |

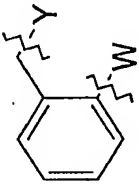
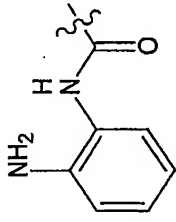
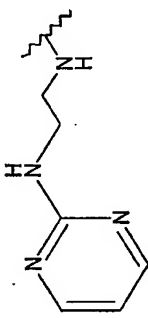
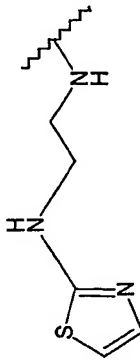
| Ex. | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|-----|-----|--|----|----|---|---|--|------|
| 353 | 498 |  | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.22 (bs, 1H), 7.17 (d, J=8.2 Hz, 2H), 6.97 (d, J=8.2 Hz, 2H), 6.93 (d, J=7.6 Hz, 1H), 6.85 (bs, 1H), 6.77 (bs, 1H), 6.60-6.53 (m, 3H), 6.43-6.40 (m, 2H), 4.97 (bs, 2H), 4.43 (bs, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 2.87-2.85 (m, 2H), 2.65-2.62 (m, 2H). | 37 |
| 354 | 499 |  | CH | CH | H | N-(2-Amino-phenyl)-3-[4-[(1H-indol-2-ylmethyl)-(3,4,5-trimethoxyphenyl)-amino]-methyl]-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 10.77 (bs, 1H), 9.39 (bs, 1H), 7.62 (d, J=7.9 Hz, 1H), 7.49 (d, J=5.7 Hz, 2H), 7.37 (d, J=7.9 Hz, 2H), 7.26 (d, J=7.9 Hz, 2H), 7.10 (t, J=7.5 Hz, 2H), 7.00-6.83 (m, 4H), 6.78 (d, J=7.9 Hz, 1H), 6.61 (t, J=7.5 Hz, 1H), 5.98 (s, 1H), 5.32 (bs, 1H), 4.98 (bs, 2H), 4.32 (d, J=5.2 Hz, 2H), 3.98 (bs, 2H), 3.73 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H). | 58 |
| 355 | 500 |  | CH | CH | H | N-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxyphenylsulfanylmethyl)-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.69 (bs, 1H), 8.04 (d, J=8.3 Hz, 2H), 7.78 (d, J=8.3 Hz, 2H), 7.58-7.55 (m, 2H), 7.06 (d, J=6.2 Hz, 1H), 6.96 (d, J=7.3 Hz, 1H), 6.90 (d, J=7.0 Hz, 1H), 6.60 (bs, 1H), 5.81 (s, 2H), 4.34 (bs, 2H), 3.78 (s, 6H), 3.67 (s, 3H). | 3, 7 |
| 356 | 501 |  | CH | CH | H | 3-[4-[(6-Acetylbenzo[1,3]dioxo-1,5-ylamino)-methyl]-phenyl]-N-(2-amino-phenyl)-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.81 (bs, 1H), 7.95 (d, J=7.9 Hz, 2H), 7.58 (d, J=7.9 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4 Hz, 1H), 7.02-7.00 (m, 2H), 6.85 (d, J=7.5 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.60 (bs, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.60 (bs, 2H), 2.50 (bs, 3H). | 58 |

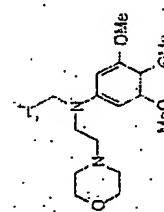
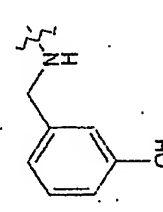
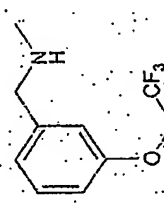
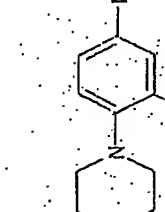
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|--|---|-------|
| 357 502 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(5-methoxybenzothiazol-2-ylamino)methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.43 (bs, 1H), 8.37 (bs, 1H), 7.66-7.57 (m, 3H), 7.49 (d, J=7.5 Hz, 2H), 7.37-7.33 (m, 3H), 6.96-6.90 (m, 1H), 6.87 (d, J= 8.8 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.63 (t, J=7.5 Hz, 1H), 4.99 (bs, 2H), 4.64 (bs, 2H), 3.37 (s, 3H). | 58 |
| 358 503 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-morpholin-4-ylphenylamino)methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (bs, 1H), 7.63-7.56 (m, 3H), 7.47 (d, J=7.9 Hz, 2H), 7.39 (d, J=7.5 Hz, 1H), 6.95 (d, J=8.3 Hz, 1H), 6.82 (bs, 1H), 6.77 (d, J=8.4 Hz, 2H), 6.66-6.56 (m, 3H), 5.91 (bs, 1H), 5.01 (bs, 2H), 4.30 (bs, 2H), 3.74 (bs, 4H), 2.93 (bs, 4H). | 58 |
| 359 504 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-(trifluoromethoxyphenylamino)methyl)-phenyl]-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (s, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 15.9 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.39 (d J=7.4 Hz, 1H), 7.10 (d, J = 8.2 Hz, 2H), 6.99 (d, J=7.1 Hz, 1H), 6.92 (d, J = 15.4 Hz, 1H), 6.81 (dd, J = 1.3, 8.0 Hz, 1H); 6.61-6.68 (m, 4H), 4.99 (s, 2H), 4.36 (d, J=6.0 Hz, 2H). | 3, 33 |

| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|---|---|-------|
| 360 505 |  | CH | CH | H | N-(2-Amino-3-phenyl-4-(benzo[1,3]dioxol-5-ylaminomethyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.59 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.1 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.81 (dd, J = 1.4, 8.0 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.62 (dd, J = 1.4, 7.7 Hz, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.05 (m, 2H), 5.87 (s, 2H), 4.99 (s, 2H), 4.29 (d, J = 6.0 Hz, 2H). | 3, 33 |
| 361 506 |  | CH | CH | H | N-(2-Amino-3-phenyl-4-(3-trifluoromethoxyphenylaminomethyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 3H), 7.48 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 8.2, 8.2 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 15.2 Hz, 1H), 6.81 (m, 2H), 6.64 (m, 2H), 6.49-6.55 (m, 2H), 5.00 (s, 2H), 4.38 (d, J = 5.3 Hz, 2H). | 3, 33 |
| 362 507 |  | CH | CH | H | N-(2-Amino-3-phenyl-4-(3-methoxyphenylaminomethyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.90-7.02 (m, 3H), 6.81 (d, J = 7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.0 Hz, 1H), 6.36 (m, 1H), 6.24 (d, J = 8.2 Hz, 1H), 6.18 (m, 2H), 5.00 (s, 2H), 4.34 (d, J = 5.3 Hz, 2H), 3.69 (s, 3H). | 3, 33 |
| 363 508 |  | CH | CH | H | N-(2-Amino-3-phenyl-4-(2-methoxyphenylaminomethyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.58 (d, J = 15.2 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.0 Hz, 1H), 6.94-7.00 (m, 1H), 6.87 (d, J = 7.6 Hz, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 7.6, 7.6 Hz, 1H), 6.56-6.66 (m, 2H), 6.45 (d, J = 7.6 Hz, 1H), 5.68 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.41 (d, J = 6.4 Hz, 2H), 3.87 (s, 3H). | 3, 33 |

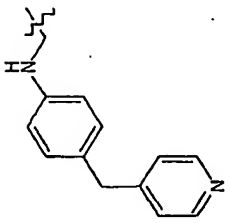
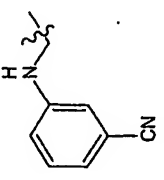
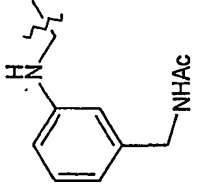
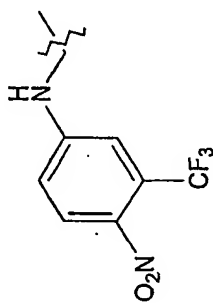
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|---|---|-------|
| 364 509 |  | CH | CH | H | N-(2-Amino-3-(4-phenylphenyl)phenyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.48 (d, J=7.9 Hz, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.10 (2d, J = 7.5, 7.5 Hz, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 16.2 Hz, 1H), 6.81 (d, J = 7.5 Hz, 1H), 6.55-6.64 (m, 4H), 6.32 (t, J = 6.0, 1H), 4.99 (s, 2H), 4.35 (d, J = 5.7 Hz, 2H). | 3, 33 |
| 365 510 |  | CH | CH | H | N-(2-Amino-3-(4-phenylphenyl)-4-isopropylphenyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 6.89-6.99 (m, 4H), 6.81 (d, J=7.6 Hz, 1H), 6.64 (dd, J = 7.0, 7.6 Hz, 1H), 6.56 (d, J = 8.2 Hz, 2H), 6.14 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.32 (d, J = 5.9 Hz, 2H), 2.76 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H). | 3, 33 |
| 366 511 |  | CH | CH | H | N-(2-Amino-3-(4-phenylphenyl)-4-biphenylphenyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.43 (s, 1H), 7.57-7.66 (m, 5H), 7.40-7.52 (m, 7H), 7.27 (dd, J = 7.0, 7.6 Hz, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.93 (d, J=15.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, 2H), 6.64 (dd, J = 7.6 Hz, 1H), 6.56 (t, J = 5.9 Hz, 1H), 4.99 (s, 2H), 4.12 (d, J = 5.9 Hz, 2H). | 3, 33 |
| 367 512 |  | CH | N | H | N-(2-Amino-3-(6-(3,4,5-trimethoxyphenylamino)pyridin-3-yl)phenyl)acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.50 (s, 1H), 8.81 (s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 15.7 Hz, 1H), 7.52 (d, J=8.2 Hz, 1H), 7.39 (d, J = 7.4 Hz, 1H), 6.96-7.05 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 7.4, 7.4 Hz, 1H), 6.26 (m, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.43 (d, J = 5.5 Hz, 2H), 3.72 (s, 6H), 3.56 (s, 3H). | 3, 33 |

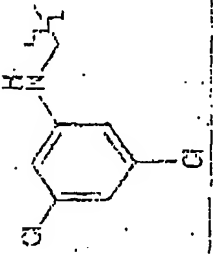
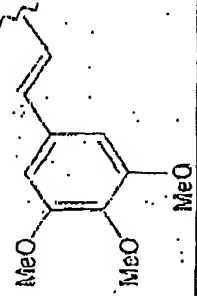
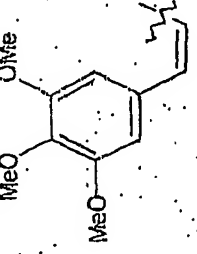
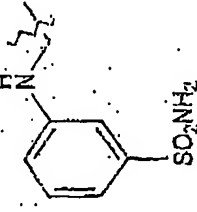
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|-----|----|----|----|---|---|---------|
| 369 514 | | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-1-methyl-1-(1-(3-benzyl-7-chloro-4-oxo-3,4-dihydroquinazolin-2-yl)-ethylamino)-2-methylphenylacrylamide | ¹ H-NMR (DMSO-d ₆) δ (ppm): 9.50 (s, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.81-7.72 (s, 3H), 7.66 (d, J = 8.1 Hz, 2H), 7.88 (d, J = 15.6 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.45-7.26 (m, 4H), 7.24-7.15 (m, 2H), 7.00-6.86 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.68 (t, J = 7.5 Hz, 1H), 5.45 (d, J = 16.8 Hz, 1H), 4.62 (bs, 1H), 4.25 (d, J = 12.9 Hz, 1H), 4.92 (d, J = 12.9 Hz, 1H), 1.91 (m, 2H), 1.28 (m, 1H), 0.90 (m, 1H), 0.72 (t, J = 7.5 Hz, 3H). | 55 |
| 371 516 | Br- | CH | CH | CH | N-(2-Amino-phenyl)-3-(4-bromo-phenyl)-1-methylphenylacrylamide | ¹ H NMR: (Acetone-d ₆) δ (ppm): 9.47 (bs, 1H), 7.72-7.56 (m, 5H), 7.39 (d, J=7.4 Hz, 1H), 7.00-6.95 (m, 2H), 6.81 (d, J=6.9 Hz, 1H), 6.64 (t, J=7.1 Hz, 1H), 5.00 (bs, 2H). | 14 |
| 372 517 | | CH | CH | CH | N-(2-Amino-phenyl)-4-(2,4,5-trimethoxybenzylamino)-benzamide | ¹ H NMR: (CD ₃ OD) δ (ppm): 7.61 (d, J=15.4 Hz, 1H), 7.44 (d, J=8.4 Hz, 2H), 7.25 (d, J=7.5 Hz, 1H), 7.10 (t, J=7.5 Hz, 1H), 7.00 (s, 1H), 6.94 (d, J=8.4 Hz, 1H), 6.81 (t, J=7.0 Hz, 1H), 6.76 (s, 1H), 6.70 (d, J=8.4 Hz, 2H), 6.92 (d, J=15.4 Hz, 1H), 4.35 (s, 2H), 3.94 (s, 3H), 3.77 (s, 3H). | 1,7, 10 |
| 373 518 | | CH | CH | CH | N-(2-Amino-phenyl)-3-(4-phenyl)-1-methyl-1-(1-(3,4,5-trimethoxyphenylamino)-ethyl)-phenylacrylamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.24 (s, 1H), 8.00 (d, J=12Hz, 1H), 7.80 (d, J=12Hz, 1H), 7.40-7.70 (m, 7H), 6.80-7.00 (m, 2H), 6.70 (d, J = 12Hz, 1H), 6.20 (s, 2H), 4.50 (m, 1H), 3.70 (s, 6H), 3.50 (s, 3H), 1.50 (d, 3H). | 58 |

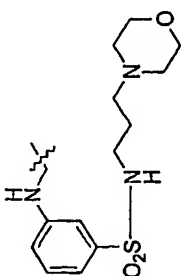
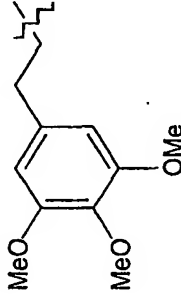
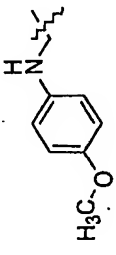
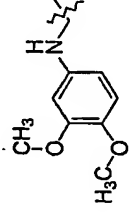
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|--|----|----|---|---|--|------|
| 374 519 |  | C | CH | H | N-(2-Amino-phenyl)-3-(9H-fluoren-2-yl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.41 (s, 1H), 8.00 (t, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.77-7.56 (m, 3H), 7.52-7.32 (m, 3H), 7.00 (d, J = 15.8 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.63 (t, J = 7.5 Hz, 1H), 5.00 (s, 2H), 4.03 (s, 2H). | 59 |
| 375 520 |  | CH | CH | H | N-(2-Amino-phenyl)-4-[2-(2-amino-phenyl)carbamoyl]-vinylbenzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.71 (s, 1H), 9.43 (s, 1H), AB system (δ _A = 8.05, δ _B = 7.75, J = 7.9 Hz, 4H), 7.62 (d, J = 15.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.05-6.88 (m, 3H), 6.78 (t, J = 7.9 Hz, 2H), 6.65-6.55 (m, 2H), 4.96 and 4.92 (2s, 4H). | 59 |
| 376 521 |  | N | CH | H | N-(2-Amino-phenyl)-3-{6-[2-(pyrimidin-2-ylamino)-ethylamino]-pyridin-3-yl}-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.29 (s, 1H), 8.32 (d, J = 4.9 Hz, 2H), 8.24 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 6.9 Hz, 1H), 7.48 (d, J = 15.7 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.26 (bs, 2H), 6.96 (t, J = 6.9 Hz, 1H), 6.80 (dd, J = 1.1, 7.7 Hz, 1H), 6.69-6.61 (m, 4H), 5.00 (s, 2H), 3.52 (bs, 4H). | 3 |
| 377 522 |  | N | CH | H | N-(2-Amino-phenyl)-3-{6-[2-(thiazol-2-ylamino)-ethylamino]-pyridin-3-yl}-acrylamide | ¹ H NMR (300 MHz, CD ₃ OD) δ (ppm): 8.12 (s, 1H), 8.08 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 15.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.4 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.75 (t, J = 7.4 Hz, 1H), 6.64 (d, J = 15.4 Hz, 1H), 6.65 (s, 1H), 4.90 (s, 5H), 3.50-3.45 (m, 4H), 3.30 (d, J = 1.3 Hz, 1H). | 3 |

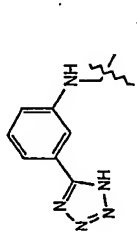
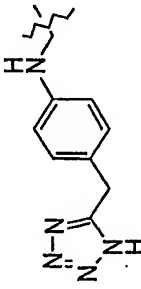
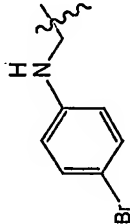
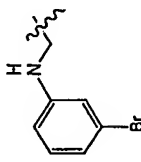
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Sch |
|---------|---|----|----|---|--|---|-----------|
| 378 523 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-3-(4-(2-morpholin-4-yl-ethyl))-4-yl-ethyl-3,4,5-trimethoxy-phenyl-amino-methyl-phenyl-acrylamide | ¹ H-NMR (CD ₃ OD), δ (ppm): 7.83 (d, J = 15.6 Hz, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.62-7.58 (m, 2H), 7.53-7.51 (m, 2H), 7.49 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 15.6 Hz, 1H), 4.99 (bs, 9H), 4.84 (bs, 2H), 4.22 (t, J = 6.5 Hz, 2H), 4.05 (s, 4H), 3.85 (s, 6H), 3.76 (s, 3H), 3.57-3.50 (m, 4H). | 3, 33, 57 |
| 379 524 |  | N | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-3-(4-(2-morpholin-4-yl-ethyl))-4-yl-ethyl-3,4,5-trimethoxy-phenyl-amino-methyl-phenyl-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.32 (s, 1H), 9.26 (s, 1H), 8.19 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.57 (t, J = 6.0 Hz, 1H), 7.41 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 7.7 Hz), 7.10 (t, J = 7.6 Hz, 1H), 6.91 (t, J = 7.6 Hz, 1H), 6.75 (m, 3H), 6.59 (m, 4H), 4.98 (bs, 2H), 4.46 (d, J = 5.8 Hz, 2H). | 3 |
| 380 525 |  | N | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-3-(4-(2-morpholin-4-yl-ethyl))-4-yl-ethyl-3,4,5-trimethoxy-phenyl-amino-methyl-phenyl-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.25 (s, 1H), 8.18 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.59 (t, J = 6.0 Hz, 1H), 7.42 (d, J = 15.7 Hz, 1H), 7.30 (m, 2H), 7.00 (m, 2H), 6.92 (m, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.60 (m, 3H), 4.92 (s, 2H), 4.73 (q, J = 8.8 Hz, 2H), 4.52 (d, J = 5.8 Hz, 2H). | 3 |
| 381 526 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-3-(4-(2-morpholin-4-yl-ethyl))-4-yl-ethyl-3,4,5-trimethoxy-phenyl-amino-methyl-phenyl-acrylamide | ¹ H-NMR (CD ₃ OD), δ (ppm): 7.64 (d, J = 15.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.49 (m, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.21 (m, 2H), 7.03 (t, J = 7.6 Hz, 1H), 6.88-6.71 (m, 4H), 4.88 (bs, 4H), 4.34 (s, 2H), 2.86 (t, J = 4.1 Hz, 4H), 2.67 (bs, 4H), 2.41 (s, 3H). | 3, 33, 58 |

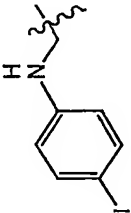
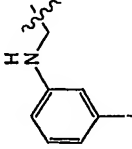
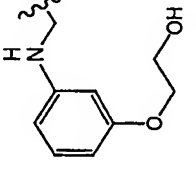
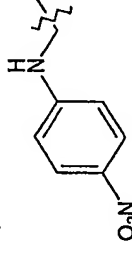
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|---|--|-----------|
| 382 527 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-([3-fluoro-4-(4-methylpiperazin-1-yl)-phenylamino]-methyl)-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.43 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.00-6.88 (m, 2H), 6.85-6.79 (m, 2H), 6.63 (t, J = 7.6 Hz, 1H), 6.44-6.30 (m, 3H), 4.99 (bs, 2H), 4.30 (d, J = 5.5 Hz, 2H), 2.87 (bs, 4H), 2.55 (m, 4H), 2.27 (s, 3H). | 3, 33, 58 |
| 383 528 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(3-hydroxyphenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 7.49 (d, J = 14.0 Hz, 1H); 7.32 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 7.2 Hz, 2H), 7.05 (m, 1H), 6.96 (m, 1H), 6.90 (m, 3H), 6.76 (m, 1H), 6.55 (d, J = 14.0 Hz, 1H), 6.03 (m, 1H), 5.99 (m, 1H), 4.30 (bs, 5H), 4.10 (s, 2H). | 3, 33 |
| 384 529 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-trifluoromethyl-2-pyrimidin-2-ylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (CD ₃ OD), δ (ppm): 7.73 (d, J = 16.0 Hz, 1H); 7.63 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.03 (dt, J = 7.7, 1.4 Hz, 1H), 6.89 (d, J = 1.1 Hz, 1H), 6.85 (m, 1H), 6.73 (dt, J = 7.7, 1.1 Hz, 1H), 6.56 (d, J = 16.0 Hz, 1H), 5.27 (s, 2H), 4.87 (bs, 2H), 4.62 (s, 2H). | 3, 33 |
| 385 530 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(3-hydroxymethylphenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.90 (s, 1H), 7.58 (m, 3H), 7.43 (d, J = 8.0 Hz, 2H); 7.37 (d, J = 8.0 Hz, 1H), 7.11 (m, 1H), 7.00 (m, 3H), 6.85 (d, J = 15.4 Hz, 1H), 6.63 (s, 1H), 6.51 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.7 Hz, 1H), 4.35 (s, 2H), 4.32 (s, 2H). | 3, 33 |

| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|---|--|-------|
| 386 531 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-pyridin-4-ylmethyl)-phenylamino]-methyl}-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.66 (s, 1H), 8.46 (d, J = 4.7 Hz, 2H); 7.55 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 15.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 4.7 Hz, 2H), 7.00 (d, J = 15.7 Hz, 1H), 6.92 (d, J = 6.9 Hz, 2H), 6.90 (m, 1H), 6.75 (d, J = 8 Hz, 1H), 6.58 (m, 2H), 6.52 (d, J = 6.9 Hz, 2H), 6.10 (bs, 1H), 4.26 (bs, 2H), 3.80 (s, 2H), 2.08 (d, J = 1.9 Hz, 2H). | 3, 33 |
| 387 532 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(3-cyano-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.38 (s, 1H), 7.58 (d, J = 7.7 Hz, 2H); 7.54 (d, J = 15.9 Hz, 1H), 7.41 (d, J = 7.7 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 6.92-6.83 (m, 5H), 6.75 (d, J = 8.0 Hz, 1H), 6.58 (t, J = 7.4 Hz, 1H), 4.95 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H). | 3, 33 |
| 388 533 |  | CH | CH | H | 3-(4-{[3-(Acetylamino)-methyl]-phenylamino}-methyl)-N-(2-amino-phenyl)-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.37 (bs, 1H), 8.21 (t, J = 5.8 Hz, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.53 (d, J = 15.7 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.1 Hz, 1H), 6.97 (m, 1H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (dd, J = 1.4, 8.0 Hz, 1H), 6.58 (dt, J = 1.4, 8.0 Hz, 1H), 6.50 (bs, 1H), 6.41 (d, J = 8.0 Hz, 2H), 6.30 (t, J = 6.0 Hz, 1H), 4.94 (bs, 2H), 4.28 (d, J = 6.0 Hz, 2H), 4.09 (d, J = 6.0 Hz, 2H), 1.83 (s, 3H). | 3, 33 |
| 389 534 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(4-nitro-3-trifluoromethyl-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.37 (bs, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.7 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.67-6.55 (m, 4H), 5.84 (t, J = 5.8 Hz, 1H), 4.94 (bs, 2H), 4.22 (d, J = 5.8 Hz, 2H). | 3, 33 |

| Ex. Cpd. | W | Y | Z | R | Name | Characterization | Solm |
|----------|--|----|----|---|--|---|----------|
| 390 535 |  | CH | CH | H | N-(2-Amino-phenyl)-3-((4-phenyl)-3-((3,5-dichlorophenylamino)-methyl)-phenyl)-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.39 (bs, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 15.7 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.3 Hz, 1H), 6.97-6.83 (m, 2H), 6.87 (d, J = 15.7 Hz, 1H), 6.75 (dd, J = 1.4, 8.0 Hz, 1H), 6.60-6.55 (m, 4H), 4.95 (bs, 2H), 4.33 (d, J = 6.0 Hz, 2H). | 3, 33 |
| 391 536 |  | CH | CH | H | N-(2-Amino-phenyl)-3-((4-phenyl)-3-((3,4,5-trimethoxyphenyl)-vinyl)-phenyl)-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 8.12 (bs, 1H), 7.64 (d, J = 14.2 Hz, 1H), 7.42 (bs, 4H), 7.23 (bs, 2H), 6.97 (d, J = 14.2 Hz, 1H), 6.94-6.82 (m, 4H), 6.70 (s, 2H), 4.11 (bs, 2H), 3.87 (s, 6H), 3.84 (s, 3H). | 3 |
| 392 537 |  | CH | CH | H | N-(2-Amino-phenyl)-3-((4-phenyl)-3-((3,4,5-trimethoxyphenyl)-vinyl)-phenyl)-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.49 (s, 1H), 7.58 (d, J = 15.7 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (m, 4H), 7.00 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 5.0 Hz, 2H), 6.69 (d, J = 5.0 Hz, 2H), 6.58 (d, J = 15.4 Hz, 1H), 6.53 (bs, 2H), 6.47 (s, 2H), 3.85 (s, 3H), 3.63 (s, 6H). | 3 |
| 393 538 |  | CH | CH | H | N-(2-Amino-phenyl)-3-((4-phenyl)-3-((3-sulfamoylphenylamino)-methyl)-phenyl)-acrylamide | ¹ H-NMR (CD ₃ OD/CDCl ₃), δ (ppm): 7.51 (d, J = 15.7 Hz, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 7.18 (dd, J = 8.0 Hz, 2H), 7.12 (d, J = 15.7 Hz, 1H), 7.10 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.83-6.66 (m, 4H), 3.93 (bs, all NH signals). | 1, 3, 33 |

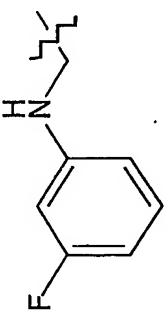
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|--|---|-----------|
| 394 539 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[3-(3-morpholin-4-yl-propyl)sulfamoyl]-phenylamino]-methyl}-phenyl)-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 8.34 (bs, 1H), 7.64 (d, J = 15.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.34 (m, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 15.4 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.04 (m, 2H), 6.74 (m, 4H), 4.85 (bs, 1H), 4.30 (d, J = 4.4 Hz, 2H), 3.69 (t, J = 5.8 Hz, 2H), 2.40 (bs, 6H), 1.59 (t, J = 4.4 Hz, 2H). | 3, 33, 42 |
| 395 540 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[2-(3,4,5-trimethoxyphenyl)-ethyl]-phenyl}-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 8.53 (s, 1H), 7.72 (d, J = 15.6 Hz, 1H), 7.38 (d, J = 7.7 Hz, 2H), 7.33 (m, 1H), 7.16 (d, J = 7.7 Hz, 2H), 7.07 (m, 1H), 6.79 (m, 2H), 6.69 (d, J = 15.6 Hz, 1H), 6.41 (s, 2H), 4.04 (bs, 2H), 3.91 (s, 3H), 3.85 (s, 6H), 2.94 (m, 4H). | 3, 32 |
| 396 541 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[4-methoxyphenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.35 (s, 1H), 7.56 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.5 Hz, 2H), 7.33 (d, J = 7.7 Hz, 1H), 6.92 (d, J = 7.7 Hz, 1H), 6.85 (d, J = 15.4 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.6 Hz, 2H), 6.58 (m, 1H), 6.52 (d, J = 8.6 Hz, 2H), 5.84 (t, J = 5.5 Hz, 1H), 4.23 (d, J = 5.5 Hz, 2H), 3.61 (s, 3H). | 3, 33 |
| 397 542 |  | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[3,4-dimethoxyphenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (CDCl ₃), δ (ppm): 8.48 (s, 1H), 7.60 (d, J = 15.4 Hz, 1H), 7.27 (m, 5H), 6.97 (t, J = 7.5 Hz, 1H), 6.70 (m, 3H), 6.59 (d, J = 15.4 Hz, 1H), 6.25 (s, 1H), 6.12 (d, J = 7.1 Hz, 1H), 4.23 (s, 2H), 3.93 (bs, 3H), 3.75 (s, 3H), 3.73 (s, 3H). | 3, 33 |

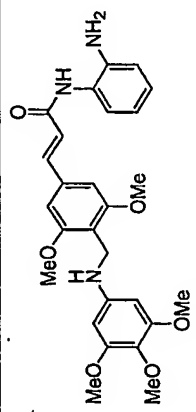
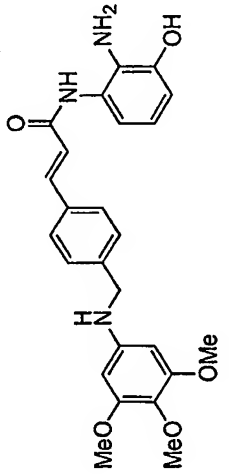
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|--|---|-------|
| 398 543 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-5-yl)-tetrazol-5-yl)-phenylamino]-methyl)-phenyl)-acrylamide | ¹ H-NMR (CD ₃ OD), δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.33 (m, 3H), 7.27 (m, 3H), 7.20 (m, 1H), 6.84 (m, 2H), 5.48 (bs, 5H), 4.46 (s, 2H). | 3, 33 |
| 399 544 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-5-yl)-tetrazol-5-yl)-methyl)-phenylamino]-methyl)-phenyl)-acrylamide | ¹ H-NMR (CD ₃ OD), δ (ppm): 7.75 (d, J = 15.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 7.29 (m, 2H), 7.20 (m, 2H), 7.04 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 15.2 Hz, 1H), 6.67 (d, J = 8.2 Hz, 2H), 5.48 (bs, 5H), 4.39 (s, 2H). 4.16 (s, 2H). | 3, 33 |
| 400 545 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-5-yl)-tetrazol-5-yl)-methyl)-phenylamino]-methyl)-phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.42 (s, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 15.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 15.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 6.66-6.57 (m, 4H), 4.99 (bs, 2H), 4.34 (d, J = 5.8 Hz, 2H). | 3, 33 |
| 401 546 |  | CH | CH | H | N-(2-Amino-phenyl)-3-(4-phenyl)-5-yl)-tetrazol-5-yl)-methyl)-phenylamino]-methyl)-phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.00-6.91 (m, 2H), 6.86 (d, J = 15.8 Hz, 1H), 6.74 (d, J = 8.2 Hz, 2H), 6.66-6.54 (m, 4H), 4.93 (bs, 2H), 4.30 (d, J = 5.3 Hz, 2H). | 3, 33 |

| Ex. | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|--|-------|
| 402 | 547 |  | CH | CH | H | N-(2-Amino-3-((4-iodophenyl)amino)phenyl)-4-iodo-N-methylphenylacrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.36 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.35 (m, 1H), 7.31 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 7.1 Hz, 1H), 6.85 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.57 (t, J = 8.0 Hz, 1H), 6.52 (t, J = 6.0 Hz, 1H), 6.42 (d, J = 8.5 Hz, 2H), 4.94 (bs, 2H), 4.28 (d, J = 6.0 Hz, 2H). | 3, 33 |
| 403 | 548 |  | CH | CH | H | N-(2-Amino-3-((4-iodophenyl)amino)phenyl)-4-iodo-N-methylphenylacrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.40 (s, 1H), 7.57 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 15.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 6.92 (m, 3H), 6.84 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 6.60-6.50 (m, 3H), 4.93 (bs, 2H), 4.28 (d, J = 5.9 Hz, 2H). | 3, 33 |
| 404 | 549 |  | CH | CH | H | N-(2-Amino-3-((4-iodophenyl)amino)phenyl)-4-iodo-N-methylphenylacrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.42 (s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 15.3 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.03-6.98 (m, 2H), 6.91 (d, J = 15.3 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.64 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 5.9 Hz, 1H), 6.28-6.22 (m, 3H), 4.99 (bs, 3H), 4.61 (s, 2H), 4.34 (d, J = 5.0 Hz, 2H), 4.28 (d, J = 5.0 Hz, 2H). | 3, 33 |
| 405 | 550 |  | CH | CH | H | N-(2-Amino-3-((4-nitrophenyl)amino)phenyl)-4-nitro-N-methylphenylacrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.38 (s, 1H), 7.99 (d, J = 9.1 Hz, 2H), 7.85 (t, J = 5.9 Hz, 1H), 7.60 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.6 Hz, 1H), 6.94-6.92 (m, 1H), 6.88 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.68 (d, J = 9.1 Hz, 2H), 6.58 (t, J = 7.6 Hz, 1H), 4.94 (bs, 2H), 4.46 (d, J = 5.9 Hz, 2H). | 3, 33 |

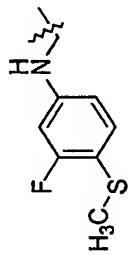
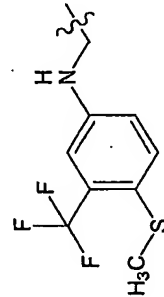
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|--|---|-------|
| 406 551 | | CH | CH | H | N-(2-Amino-3-((4-nitrophenyl)amino)phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.37 (s, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 15.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.36-7.28 (m, 4H), 7.05-6.98 (m, 2H), 6.92 (d, J = 7.6 Hz, 1H), 6.88 (d, J = 15.2 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.58 (t, J = 7.6 Hz, 1H), 4.96 (bs, 2H), 4.39 (d, J = 5.3 Hz, 2H). | 3, 33 |
| 407 552 | | CH | CH | H | N-(2-Amino-3-((4-chlorophenyl)amino)phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.43 (s, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 15.8 Hz, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 6.93 (d, J = 15.8 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.62 (d, J = 8.8 Hz, 2H), 6.55 (bs, 2H), 4.99 (bs, 2H), 4.46 (d, J = 5.9 Hz, 2H), 4.35 (d, J = 5.9 Hz, 2H). | 3, 33 |
| 408 553 | | CH | CH | H | N-(2-Amino-3-((3-chlorophenyl)amino)phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.50 (s, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.43 (m, 1H), 6.93 (d, J = 7.0 Hz, 1H), 6.79 (d, J = 15.4 Hz, 1H), 6.68 (m, 3H), 6.59 (m, 3H), 5.24 (bs, 2H), 4.31 (s, 2H). | 3, 33 |
| 409 554 | | CH | CH | H | N-(2-Amino-3-((4-fluorophenyl)amino)phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.37 (s, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 15.4 Hz, 1H), 7.47 (d, J = 7.6 Hz, 2H), 7.41 (m, 1H), 7.01-6.90 (m, 4H), 6.75 (d, J = 7.6 Hz, 1H), 6.67-6.59 (m, 3H), 6.27 (bs, 1H), 4.95 (bs, 2H), 4.27 (s, 2H). | 3, 33 |

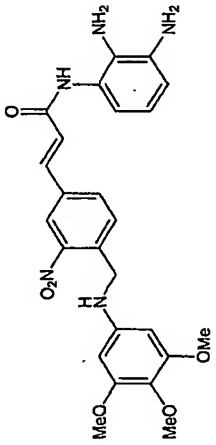
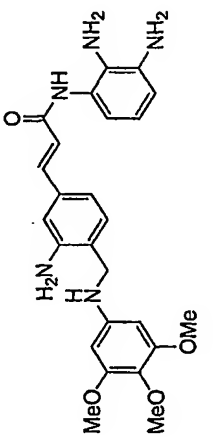
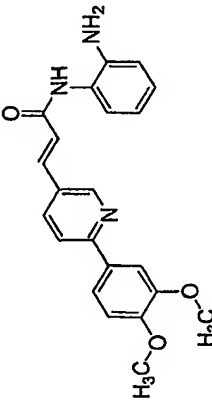
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|----|---|---|--|-------|
| 410 555 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-(3-methylsulfonyl-phenylamino)-methyl}-phenyl}-acrylamide | ¹ H NMR (300 MHz, CD ₃ OD) δ (ppm): 7.64 (d, J = 15.9 Hz, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.56 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 6.37 (d, J = 7.8 Hz, 1H), 4.29 (s, 2H), 4.05 (bs, 4H), 2.37 (s, 3H). | 3, 33 |
| 411 556 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-(3-methylsulfonyl-phenylamino)-methyl}-phenyl}-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.36 (s, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 15.8 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 7.9 Hz, 1H), 7.07 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 15.8 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.60-6.54 (m, 3H), 6.39 (t, J = 5.7 Hz, 1H), 4.93 (bs, 2H), 4.29 (d, J = 6.1 Hz, 2H), 2.32 (s, 3H). | 3, 33 |
| 412 557 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-(5-bromo-pyridin-2-ylamino)-methyl}-phenyl}-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.36 (s, 1H), 8.02 (d, J = 1.7 Hz, 1H), 7.57-7.50 (m, 4H), 7.38-7.32 (m, 4H), 6.92 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 16.3 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 9.2 Hz, 1H), 4.94 (bs, 2H), 4.48 (d, J = 5.7 Hz, 2H). | 3, 33 |
| 413 558 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-(naphthalen-1-ylaminomethyl)-phenyl}-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.37 (s, 1H), 8.25 (m, 1H), 7.76 (m, 1H), 7.57 (m, 2H), 7.47 (m, 4H), 7.33 (d, J = 7.0 Hz, 1H), 7.17 (m, 1H), 7.07 (d, J = 8.2 Hz, 1H), 6.99 (t, J = 5.3 Hz, 1H), 6.92 (d, J = 7.0 Hz, 1H), 6.85 (d, J = 16.4 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.57 (t, J = 7.6 Hz, 1H), 6.36 (t, J = 7.6 Hz, 1H), 4.90 (s, 2H), 4.54 (d, J = 5.3 Hz, 2H). | 3, 33 |

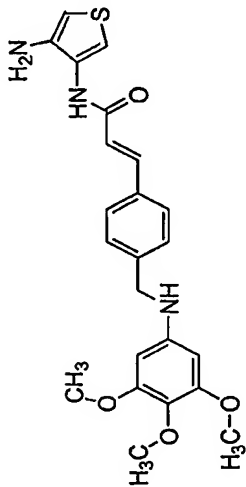
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|---|----|---|---|--|---|-------|
| 414 559 |  | CH | | | N-(2-Amino-3-((4-(3-fluorophenyl)-3-fluorophenylamino)methyl)-phenyl)-acrylamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.39 (s, 1H), 7.57 (d, J = 7.0 Hz, 2H), 7.53 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.02 (q, J = 7.6 Hz, 1H), 6.90 (m, 2H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (m, 1H), 6.40 (d, J = 8.2 Hz, 1H), 6.29 (m, 2H), 4.90 (s, 1H), 4.29 (bs, 2H), 4.02 (s, 2H). | 3, 33 |

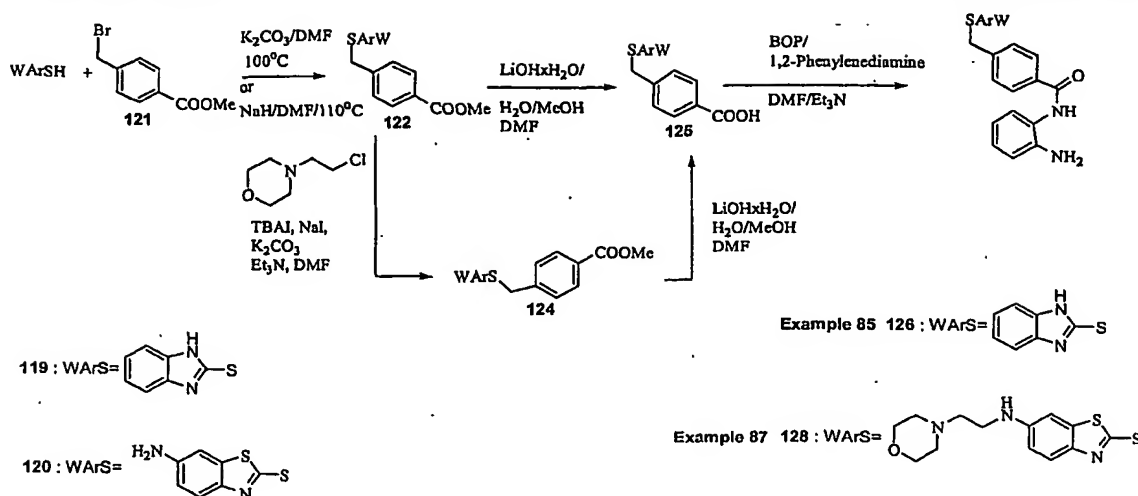
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|--|---|---|---|---|--|-------|
| 415 560 |  | | | | N-(2-Amino-3-((3,5-dimethoxy-4-((3,4,5-trimethoxyphenylamino)methyl)-phenyl)-acrylamide | ¹ H-NMR (CDCl ₃) δ (ppm): 7.73 (bs, 1H), 7.63 (d, J = 14.9 Hz, 1H), 6.81 (m, 3H), 6.70 (m, 2H), 6.68-6.56 (m, 2H), 6.07 (s, 2H), 4.35 (s, 2H), 3.86 (s, 6H), 3.81 (s, 6H), 3.75 (s, 3H). | 60 |
| Ex. Cpd | W | Y | Z | R | Name | Characterization | Schm |
| 416 561 |  | | | | N-(2-Amino-3-((3,4,5-trimethoxyphenyl)-acrylamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 9.22 (s, 1H), 9.11 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.64 (d, J = 15.8 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 6.96 (d, J = 15.8 Hz, 1H), 6.78 (t, J = 7.9 Hz, 1H), 6.23 (t, J = 7.9 Hz, 1H), 6.16 (d, J = 7.9 Hz, 1H), 6.09 (t, J = 6.2 Hz, 1H), 5.89 (s, 2H), 4.77 (bs, 2H), 4.27 (d, J = 5.7 Hz, 2H), 5.89 (s, 6H), 5.76 (s, 3H). | 3, 33 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|-----|---|----|----|---|--|--|----------|
| 41 7 | 562 | | CH | CH | H | N-(2-Amino-phenyl)-3-{4-[(2,3,4-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.25 (s, 1H), 7.74 (d, J = 15.5 Hz, 1H), 7.44 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.34-7.29 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 6.82 (t, J = 7.5 Hz, 1H), 6.79 (m, 1H), 6.66 (d, J = 8.8 Hz, 1H), 6.31 (d, J = 8.8 Hz, 1H), 4.36 (s, 2H), 4.18 (bs, 2H), 3.98 (s, 3H), 3.96 (s, 3H), 3.84 (s, 3H). | 3, 33 |
| 41 8 | 563 | | CH | CH | H | N-(2-Amino-phenyl)-3-[4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl]-acrylamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.58 (s, 1H), 7.66 (d, J = 15.4 Hz, 1H), 7.33-7.28 (m, 3H), 7.23 (d, J = 7.0 Hz, 2H), 7.04 (t, J = 7.0 Hz, 1H), 6.77-6.70 (m, 4H), 6.64 (d, J = 15.4 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 5.90 (s, 2H), 4.27 (s, 2H), 4.25 (s, 2H), 4.08 (bs, 4H), 3.82 (s, 6H), 3.77 (s, 6H). | 3, 33 |
| 41 9 | 564 | | | | | N-(2,3-Diamino-phenyl)-3-{4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 7.64 (d, J = 15.4 Hz, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.31-7.24 (m, 2H), 6.86 (s, 1H), 6.73 (d, J = 15.4 Hz, 1H), 5.84 (s, 2H), 4.27 (s, 2H), 4.00 (bs, 6H), 3.71 (s, 6H), 3.68 (s, 3H). | 3, 33 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|-----|---|----|----|---|---|---|----------|
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
| 42 0 | 565 |  | CH | CH | H | N-(2-Amino-4-fluoro-3-{4-[(3-methylsulfanyl-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.38 (bs, 1H), 7.58 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 15.4 Hz, 1H), 7.40 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.14 (t, J = 8.3 Hz, 1H), 6.94-6.89 (m, 2H), 6.81 (d, J = 15.7 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.43-6.38 (m, 2H), 4.94 (bs, 2H), 4.30 (d, J = 5.7 Hz, 2H), 2.28 (s, 3H). | 3, 33 |
| 42 1 | 566 |  | CH | CH | H | N-(2-Amino-4-fluoro-3-{4-[(3-methylsulfanyl-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.39 (bs, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 15.8 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.36 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 6.2 Hz, 1H), 6.96-6.90 (m, 4H), 6.82 (d, J = 15.8 Hz, 1H), 6.79-6.74 (m, 1H), 6.58 (t, J = 7.5 Hz, 1H), 4.95 (bs, 2H), 4.35 (d, J = 6.2 Hz, 2H), 2.35 (s, 3H). | 3, 33 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|---------|-----|--|---|---|---|--|--|-----------------|
| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
| 42 2 | 567 |  | | | | N-(2-Amino-phenyl)-3-[(3,4,5-nitro-4-[(3,4,5-trimethoxyphenylamino)-methyl]-phenyl)-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.50 (s, 1H), 8.09 (s, 1H), 7.80 (d, J = 15.4 Hz, 1H), 7.81 (s, 2H), 7.34 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 6.88 (d, J = 15.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.26 (t, J = 6.2 Hz, 1H), 5.90 (s, 2H), 4.96 (bs, 2H), 4.39 (d, J = 5.7 Hz, 2H), 3.66 (s, 6H), 3.51 (s, 3H). | 3, 33 |
| 42 3 | 568 |  | | | | N-(2-Amino-phenyl)-3-[(3,4,5-amino-4-[(3,4,5-trimethoxyphenylamino)-methyl]-phenyl)-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.29 (s, 1H), 7.72 (d, J = 15.4 Hz, 1H), 7.33 (m, 2H), 6.90 (1H); 6.71 (2H), 6.62 (3H), 5.97 (1H), 5.87 (2H), 5.49 (2H), 4.96 (2H), 4.10 (2H), 3.65 (6H), 3.51 (3H). | 3, 33 |
| 42 4 | 569 |  | | | | N-(2-Amino-phenyl)-3-[(6-(3,4-dimethoxyphenyl)-pyridin-3-yl)-acrylamide | LRMS: calc: 375.4, found: 376.4 | 3, 15, 33 |

| Ex | Cpd | W | Y | Z | R | Name | Characterization | Schm |
|----|-----|---|---|---|---|---|---|-----------|
| 4 | 2 |  | | | | N-(4-Amino-thiophen-3-yl)-3-{4-[(4-morpholin-4-yl-phenylamino)-methyl]-phenyl}-acrylamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.64 (bs, 1H), 7.65 (d, J=7.9 Hz, 2H), 7.60 (d, J=14.0 Hz, 1H), 7.50 (d, J=7.9 Hz, 2H), 6.90 (d, J=15.8 Hz, 1H), 6.15 (d, J=4.0 Hz, 1H), 5.95 (s, 2H), 5.82 (s, 1H), 4.89 (bs, 2H), 4.33 (d, J=5.7 Hz, 2H), 3.71 (s, 6H), 3.57 (s, 3H). | 3, 33, 60 |
| 5 | 570 | | | | | | | |
| | | | | | | | | |



Example 85

***N*-(2-Amino-phenyl)-4-(1*H*-benzimidazol-2-ylsulfanylmethyl)-benzamide (compound 126)**

Step 1: 4-(1*H*-Benzimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (compound 122)

[0215] Following the procedure described in Example 47, step 2, but using 119 and substituting 121 for 63, the title compound 122 was obtained in 95% yield. LRMS = 299.1 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(1*H*-benzimidazol-2-ylsulfanylmethyl)-benzamide (126)

[0216] Following the procedure described in Example 1, steps 4 and 5, but substituting 122 for 6, the title compound 126 was obtained in 62% yield. ¹H NMR: (DMSO-d₆) δ (ppm): 9.57 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.53 (bs, 2H), 7.36 (bs, 2H), 7.14-7.08 (m, 3H), 6.94 (t, J = 8.2 Hz, 1H), 6.74 (d, J = 6.9 Hz, 1H), 6.56 (t, J = 8.0 Hz, 1H), 4.87 (bs, 2H), 4.62 (s, 2H).

Example 87

***N*-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound 128)**

Step 1: 4-(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester (122)

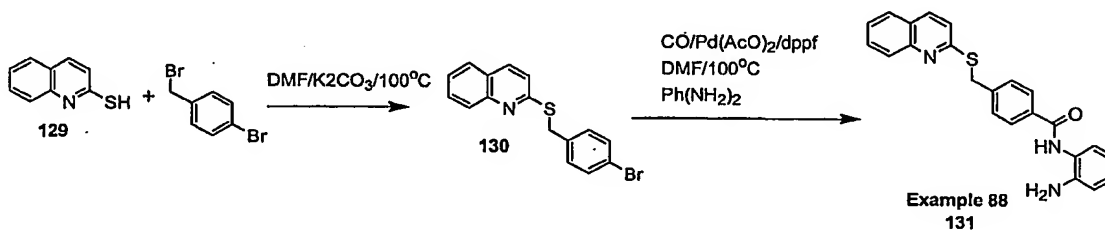
[0217] Following the procedure described in Example 47, step 2, but using 120 and substituting 121 for 63, the title compound 122 was obtained in 45% yield. LRMS = 331.0 (M+1).

Step 2: 4-[6-(2-Morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (compound 124)

[0218] To a solution of 4-(6-Amino-benzothiazol-2-ylsulfanylmethyl)-benzoic acid methyl ester **122** (800 mg, 2.42 mmol), in DMF (24 mL), were added successively solid 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol), K_2CO_3 (611 mg, 5.08 mmol), NaI (363 mg, 2.42 mmol), Et_3N (370 μ L, 2.66 mmol) and tetrabutylammonium iodide (894 mg, 2.42 mmol). The mixture was stirred at 120°C for 24h and more 4-(2-chloroethyl)morpholine hydrochloride (296 mg, 2.66 mmol) was added. The mixture was stirred for 8h at 120°C and the solvent was removed in vacuo. The resulting black syrup was partitioned between H_2O and EtOAc. The organic layer was successively washed with HCl 1N and saturated aqueous $NaHCO_3$. The precipitate was extracted twice with EtOAc, dried over $MgSO_4$ and concentrated. Purification by flash chromatography (MeOH/ $CHCl_3$, 5:95 to 10:90) afforded 48 mg (4% yield) of **124** as a light yellow oil. LRMS = 444.1 (M+1).

Step 3: N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethylamino)-benzothiazol-2-ylsulfanylmethyl]-benzamide (compound 128)

[0219] Following the procedure described in Example 1, steps 4 and 5, but substituting **124** for **6**, the title compound **128** was obtained in 76% yield. 1H NMR: (Acetone- d_6) δ (ppm): 9.06 (bs, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.2 Hz, 1H), 7.02-6.97 (m, 1H), 6.87-6.82 (m, 2H), 6.66 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.63 (s, 2H), 3.64-3.60 (m, 4H), 3.25 (t, J = 6.3 Hz, 2H), 2.63 (t, J = 6.3 Hz, 2H), 2.54-2.42 (m, 4H).



Example 88

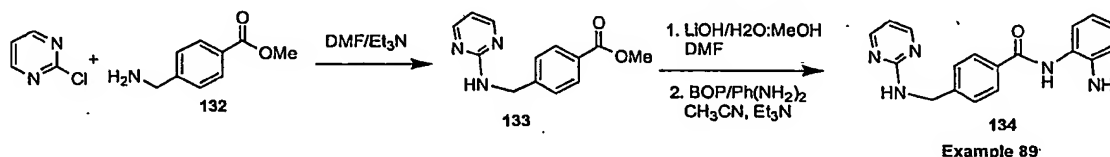
N-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (compound 131)

Step 1: 2-(4-Bromo-benzylsulfanyl)-quinoline (compound 130)

[0220] Following the procedure described in Example 47, step 2, but substituting 129 for 63, the title compound 130 was obtained in 89% yield. LRMS = 332.0 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(quinolin-2-ylsulfanylmethyl)-benzamide (131)

[0221] Following the procedure described in Example 40, step 2, but substituting 129 for 42, the title compound 131 was obtained in 70% yield. ¹H NMR: (DMSO-d₆) δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H).



Example 89

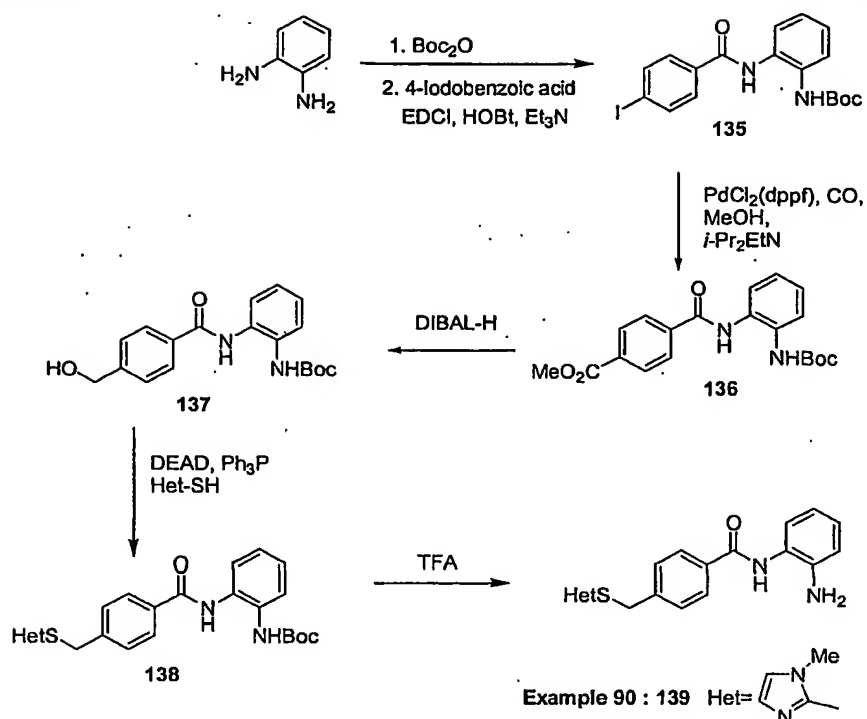
N-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (compound 134)

Step 1: 4-(Pyrimidin-2-ylaminomethyl)-benzoic acid methyl ester (compound 133)

[0222] Following the procedure described in Example 47, step 2, but substituting 132 for 63, the title compound 133 was obtained in 76% yield. LRMS = 244.2 (M+1).

Step 2: *N*-(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide (134)

[0223] Following the procedure described in Example 1, steps 4 and 5, but substituting 129 for 6, the title compound 134 was obtained in 91% yield. ¹H NMR: (DMSO-d₆) δ (ppm): 9.6 (bs, 1H), 8.32 (d, J = 4.9 Hz, 2H), 7.97 (dt, J = 9.9 Hz, 7.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H).

**Example 90**

N-(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)-benzamide (compound 139)

Step 1: [2-(4-Iodo-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (compound 135)

[0224] To a solution of di-tert-butylidicarbonate (39 g, 181 mmol) in THF (139 mL) placed in a water bath, was added 1,2-phenylenediamine (15 g, 139 mmol) and DMAP (1.7 g, 14 mmol). The mixture was stirred at r.t. for 16 h and the solvent was removed *in vacuo*. The crude material was partitioned between EtOAc and water. The organic layer was washed with HCl 1 N and then with aqueous saturated NaHCO₃. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated affording the compound (18.9 g, 65% yield) as a light beige powder. LRMS = 209.1 (M+1).

[0225] To a solution of 4-iodobenzoic acid (8.0 g, 32.3 mmol) in DMF (65 mL) at r.t., were successively added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (8.0 g, 41.9 mmol) and 1-hydroxybenzotriazole (5.2 g, 38.7 mmol). The mixture was stirred for 1 h and a solution of (2-amino-phenyl)-carbamic acid tert-butyl ester (6.3 g, 30.2 mmol) in DMF (20 mL) was added to the mixture *via* cannula, followed by triethylamine (5.9 mL, 4.9 mmol). The mixture

was stirred for 16 h and the solvent was removed in vacuo. The crude material was partitioned between chloroform and water. The organic layer was washed with aqueous saturated NaHCO_3 , dried over MgSO_4 and concentrated to a light brown syrup which was crystallized in hot EtOAc or Et_2O , yielding 135 (9.3 g, 70% yield) as a white solid.

LRMS = 461.0 ($\text{M}+\text{Na}^+$).

Step 2: N-[2-tert-butoxycarbonylamino-phenyl]-terephthalamic acid methyl ester (compound 136)

[0226] Following the procedure described in Example 40, step 2, but substituting 135 for 42, the title compound 136 was obtained in 95% yield. LRMS = 393.1 ($\text{M}+\text{Na}^+$).

Step 3: [2-(4-Hydroxymethyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (137)

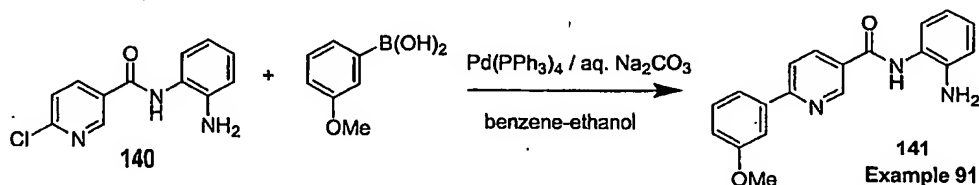
[0227] To a solution of 136 (7.5g, 20.6 mmol) in THF (40 mL), cooled down to -20°C under N_2 , was added a 1M solution of DIBAL-H (122 mL, 122 mmol) in toluene. After stirring for 18 h. at r.t., the mixture was cooled down to 0°C and carefully quenched by a dropwise addition of H_2O (10 mL) and of 2N NaOH (5 mL). The aluminum salts were allowed to decant and the supernatant was removed. The organic layer was washed with H_2O , 1 N HCl (6 times), satd. aqueous NaHCO_3 , brine, dried over MgSO_4 and concentrated (2.04 g, 43%). Purification of the crude material by flash chromatography (EtOAc/hexanes 50:50 to 70:30) afforded 137 (1.14 g, 16% yield) as a solid foam. LRMS = 365.2 ($\text{M}+\text{Na}^+$).

Step 4: {2-[4-(1-Methyl-imidazol-2-ylsulfanylmethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (compound 138)

[0228] To a solution of N-methyl-2-mercaptoimidazole (28 mg, 0.25 mmol) in THF (1 mL), at r.t. under N_2 atmosphere were successively added 137 (70 mg, 0.20 mmol), triphenylphosphine (70 mg, 0.27 mmol) followed by dropwise addition of diethyl azodicarboxylate (48 μL , 0.31 mmol). The mixture was stirred for 2 h and the solvent was removed in vacuo. Purification by flash chromatography using MeOH/ CHCl_3 (5:95) as the eluent afforded the title compound 138 (81 mg), in 91% yield, which was found to contain some diethyl hydrazodicarboxylate residus. The compound was used as is without further purification.

Step 5: *N*-(2-Amino-phenyl)-4-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)-benzamide (compound 139)

[0229] Following the procedure described in Example 42, step 3, but substituting 138 for 46, the title compound 139 was obtained in 62% yield. ¹H NMR: (Acetone-d₆) δ (ppm): 9.07 (bs, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 1.1 Hz, 1H), 7.03-6.96 (m, 2H), 6.86 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.67 (dt, J = 7.4 Hz, 1.1 Hz, 1H), 4.63 (bs, 2H), 4.29 (s, 2H), 3.42 (s, 3H).

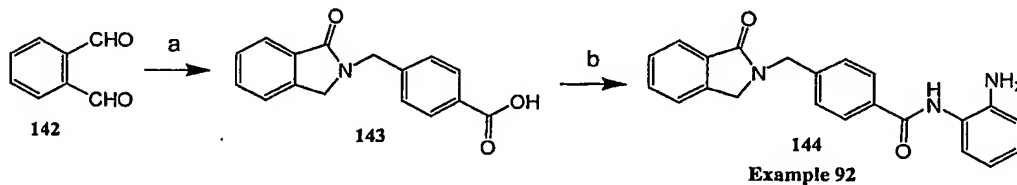


Example 91

N-(2-Amino-phenyl)-6-(3-methoxyphenyl)-nicotinamide (compound 141)

[0230] To a mixture of 3-methoxyphenyl boronic acid (152 mg, 1.0 mmol) and 140 (248 g, 1.0 mmol) were added benzene (8 mL) and ethanol (4 mL) followed by 2 M Na₂CO₃ aqueous solution (3.2 mL, 6.4 mmol). The reaction mixture was stirred under nitrogen for 30 min and then Pd(PPh₃)₄ (58 mg, 0.05 mmol) was quickly added. After 24 h of reflux, the mixture was cooled to room temperature, filtered through a pad of celite and rinsed with ethyl acetate (30 mL). The organic solution was washed with brine (5 mL), dried (MgSO₄), and concentrated.

Purification by flash silica gel chromatography (Hexane/Ethyl acetate: 1/1) afforded 141 (302 mg, 95% yield). ¹H NMR (CDCl₃) δ (ppm): 9.11 (d, J = 1.8 Hz, 1H), 8.30 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.52-7.47 (m, 1H), 7.36 (m, 1H), 7.22 (m, 1H), 7.09-6.78 (m, 4H), 3.84 (s, 3H), 3.39 (br s, 2H).



a. p-aminomethylbenzoic acid/AcOH/5 min/reflux
b. HOBT/EDC/1,2-diamino benzene

Example 92

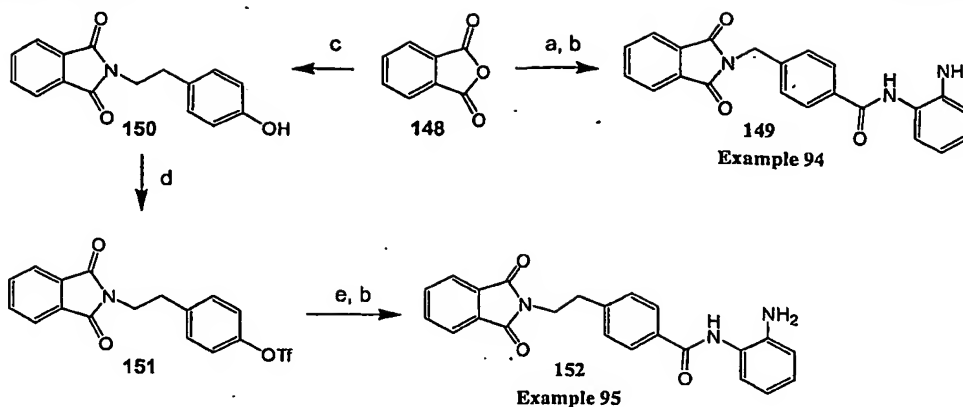
N-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide
(compound 144)

Step 1: 4-(1-Oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzoic acid
(compound 143)

[0231] To a solution of benzene-1,2-carbaldehyde 142 (1.0 g, 7.46 mmol) in 10 mL of acetic acid was added 4-aminomethylbenzoic acid (1.13 g, 7.46 mmol). The reaction mixture was refluxed 5 min and cooled to the room temperature. A crystalline precipitate was formed and triturated with CH₂Cl₂ to produce the title compound 143 (1.29 g, 49%).

Step 2: *N*-(2-Amino-phenyl)-4-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 144)

[0232] To a solution of the carboxylic acid (0.32 g, 0.89 mmol) in DMF (8 mL) at rt, was added HOBt (0.16 g, 1.15 mmol) and EDC (0.25 g, 1.33 mmol) and the solution was stirred for 1.5 h. Lastly, phenylenediamine (0.12 g, 1.07 mmol) was added and the mixture was allowed to stir for 18-20 h. DMF was removed *in vacuo* and the crude was partitioned between ethyl acetate and H₂O. The organic layer was dried over Na₂SO₄ and concentrated. Purification by column chromatography (CH₂Cl₂-MeOH (19:1)) afforded 144 in 46% yield. ¹H NMR: (DMSO-d₆) δ 9.71 (s, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.55-7.70 (m, 3H), 7.46 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.65 (t, J = 7.4 Hz, 1H), 4.93 (bs, 2 H), 4.87 (s, 2 H), 4.47 (s, 2H).



- a. p-aminomethylbenzoic acid/AcOH/reflux/3 hrs
- b. HOBt/EDC/1,2-diamino benzene
- c. 4-(2-aminoethyl)phenol/AcOH/5 hrs/reflux
- d. PhNTf₂/NaH/THF-DMF/30 min/0°C
- e. 1. CO/Pd(OAc)₂/dppf/Et₃N/MeOH-DMF/4 days/75°C
2. AcOH/HCl/3 hrs/reflux

Example 94

N-(2-Amino-phenyl)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-benzamide (compound 149)

[0233] Phthalic anhydride 148 (1.3 g, 8.9 mmol) and 4-aminomethylbenzoic acid in 20 mL acetic acid were refluxing for 3 h, cooled to the room temperature and evaporated to yield a solid residue which was triturated with water, filtered off and dried to produce the intermediate carboxylic acid (1.7 g, 68%). LMRS = 282.0 (M+1).

[0234] Following a procedure analogous to that described in Example 92, step 2, but substituting the acid for 143, the title compound 149 was obtained in 17% yield. ¹H NMR: (DMSO d₆) δ 9.59 (s, 1H), 7.82–7.91 (m, 6H), 7.40 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.55 (t, J = 7.4 Hz, 1H), 4.83 (bs, 4H).

Example 95

N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)

Step 1: 2-[2-(4-Hydroxy-phenyl)-ethyl]-isoindole-1,3-dione (compound 150)

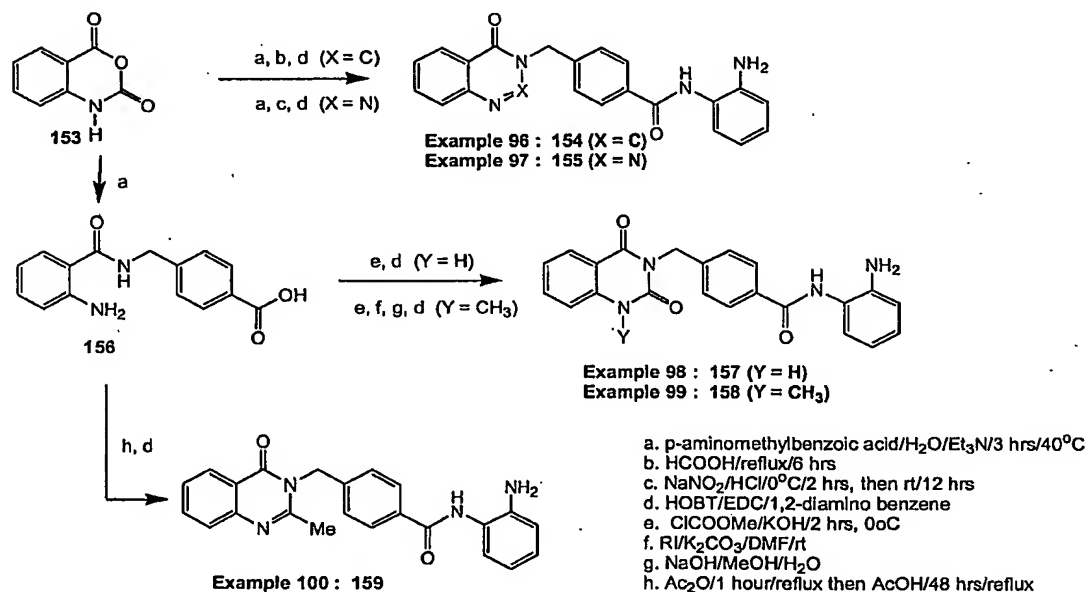
[0235] Following a procedure analogous to that described in Example 94, step 1, but substituting 4-aminomethylbenzoic acid for tyramine the title compound 150 was obtained in 48% yield. LMRS = 268.0 (M+1).

Step 2: 4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)ethyl]-phenyl trifluoromethane-sulfonate (151)

[0236] To a solution of sodium hydride (90 mg, 25 mmol) in dry THF (20 mL) at 0°C, 150 (500 mg, 8.9 mmol) was added followed by the addition of dry DMF (2 mL). The reaction mixture was stirred for 20 min at 0°C, treated portionwise with PhN(Tf)₂, stirred for additional 2 h and evaporated to produce a solid material which was purified by chromatography on a silica gel column, (CH₂Cl₂ - MeOH (19:1)) to provide 151 (639 mg, 86% yield). LMRS = 400.0 (M+1).

Step 3: N-(2-Amino-phenyl)-4-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-benzamide (compound 152)

[0237] Following a procedure analogous to that described in Example 40, step 2, but substituting 151 for 42, the title compound 152 was obtained in 15% yield. ¹H NMR: (DMSO d₆) δ 9.57 (s, 1H), 7.78-7.87 (m, 6H), 7.31 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 6.9 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.83 (bs, 2 H), 3.85 (t, J = 7.1 Hz, 2 H), 3.00 (t, J = 7.1 Hz, 2 H).



Example 96

N-(2-Amino-phenyl)-4-(4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 154)

[0238] A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et₃N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride 153 (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and evaporated to form an oily

residue, which was refluxing in formic acid (20 mL) for 7 h. Formic acid was removed in vacuum to produce a solid, which was triturated with water and filtered off to provide the carboxylic acid (1.61 g, 96%). LMRS = 281.0 (M+1).

[0239] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 154 was obtained in 43% yield. ¹H NMR: (DMSO d₆) □ 9.71 (s, 1H), 8.68 (s, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.0, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.63 (t, J = 7.4, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.22 (d, J = 7.4 Hz, 1H), 7.04 (t, J = 7.1 Hz, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 5.35 (s, 2 H).

Example 97

N-(2-Amino-phenyl)-4-(4-oxo-4H-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide (compound 155)

[0240] A suspension of 4-aminomethyl benzoic acid (1.00 g, 6.60 mmol) in water (20 mL) was treated with Et₃N (0.86 mL, 6.60 mmol) followed by the addition of isatoic anhydride (980 mg, 6.00 mmol). The reaction mixture was heated 3 h at 40°C and cooled to 0°C. The cold reaction mixture was acidified with conc. HCl (5 mL) and treated drop wise with NaNO₂ solution (520 mg, 7.5 mmol in 5 mL water) over 5 min period of time, then left overnight at room temperature. A precipitate formed which was collected, washed with water and dried to provide the carboxylic acid (1.62 g, 96%). LMRS = 282.0 (M+1).

[0241] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 155 was obtained in 27% yield. ¹H NMR: (DMSO d₆) □ 9.62 (s, 1H), 8.25 (t, J = 6.7 Hz, 2H), 8.11 (ddd, J = 7.1 Hz, 1.4 Hz, 1H), 7.93-7.98 (m, 3H), 7.49 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.7 Hz, 1H), 6.94 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.66 (s, 2 H), 4.87 (bs, 2 H).

Example 98

N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 157)

Step 1: 4-[(2-Amino-benzoylamino)-methyl]-benzoic acid (compound 156)

[0242] To a suspension of 4-aminomethylbenzoic acid (5.09 g, 33.7 mmol) in H₂O (50 mL), was added Et₃N (4.7 mL, 33.7 mmol) followed by isatoic anhydride 153 (5.0 g, 30.6 mmol). The brown mixture was heated

at 40°C for 2 h until the mixture became homogeneous and then Et₃N was removed in vacuo. The resulting aqueous solution was acidified (10% HCl/H₂O) and the mixture was partitioned between H₂O and ethyl acetate. The combined organic extracts were dried over Na₂SO₄, filtered and evaporated to give 156 as a white solid (6.0 g, 72 %). LMRS = 271.0 (M+1).

Step 2: N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 157)

[0243] The carboxylic acid 156 (1.72 g, 6.36 mmol) was suspended in a solution of NaOH (2.55 g, 63.6 mmol) in H₂O (12 mL). To this solution was added dioxane (10 mL) until mixture became homogeneous. The solution was cooled to 0°C in an ice-bath and methyl chloroformate (1.25 mL, 16.1 mmol) was added portionwise over 2 h. After completion of the reaction, the excess methyl chloroformate and dioxane were removed in vacuo and the mixture was diluted with methanol (80 mL) and H₂O (20 mL). The solution was heated to 50°C for 1 h. until the cyclization was complete. Methanol was removed in vacuo and then the aqueous layer was extracted with ethyl acetate. Subsequently, the aqueous phase was acidified (10% HCl/H₂O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were combined, dried over Na₂SO₄, filtered and evaporated to dryness. The resulting crude was triturated with warm methanol to afford the carboxylic acid as a white solid (1.7 g, 90%). LMRS = 319.0 (M+Na).

[0244] Following a procedure analogous to that described in Example 92, step 2, but substituting the quinazolinedione carboxylic acid for 143, the title compound 157 was obtained. ¹H NMR: (DMSO-d₆) δ 11.56 (brs, 1H), 9.59 (brs, 1H), 7.96-7.88 (m, 3H), 7.67 (dt, J = 8.4, 1.4 Hz, 1H), 7.30 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 7.5 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92 (dt, J = 6.9, 1.2 Hz, 1H), 6.75 (d, J = 6.9 Hz, 1H), 6.57 (t, J = 6.9 Hz, 1H), 5.15 (brs, 2H), 4.86 (brs, 2H).

Example 99

N-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 158)

Step 2: 4-(1-Methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid methyl ester

[0245] To a solution of the quinazolinedione carboxylic acid (1.0 g, 3.38 mmol) in DMF (7 mL), was added K₂CO₃ (1.4 g, 10.1 mmol) and the mixture was then cooled to 0°C. Subsequently, MeI (1.05 mL, 16.9

mmol) was added and the mixture was allowed to warm to rt in the ice bath overnight. Excess methyl iodide and DMF were removed *in vacuo* and the crude was partitioned between ethyl acetate and H₂O. The aqueous phase was washed again with ethyl acetate, the combined organic extracts were dried over Na₂SO₄ and then concentrated *in vacuo* to yield the desired product as an off-white solid (0.93 g, 85%). LMRS = 325.0 (M+1).

Step 3: 4-(1-Methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid

[0246] To a suspension of the methyl ester (1.25 g, 3.85 mmol) in methanol (35 mL), was added 1N NaOH (30 mL, 38.5 mmol) and the mixture was heated to 45-50°C for 3 h. until it became homogeneous. Methanol was removed *in vacuo* and the crude was partitioned between ethyl acetate and H₂O. The aqueous phase was acidified (10% HCl/H₂O) and extracted with ethyl acetate (2 X 300 mL). These organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford product 5 as a white solid (1.15 g, 96%). LMRS = 311.0 (M+1).

Step 4: N-(2-Amino-phenyl)-4-(1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide (compound 158)

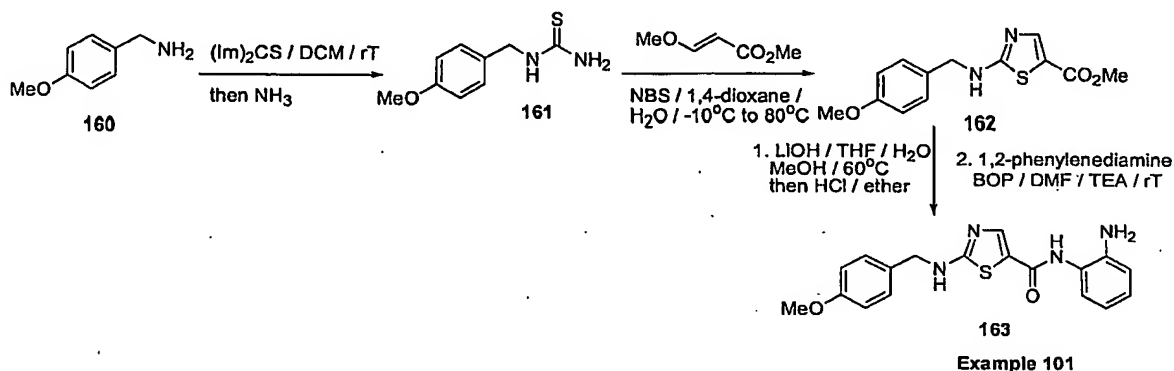
[0247] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 158 was obtained in 10% yield. ¹H NMR: (DMSO-d₆) δ 9.59 (brs, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 2H) 7.80 (dt, J = 6.9, 1.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.57 (t, J = 7.5 Hz, 1H), 5.21 (brs, 2H), 4.86 (brs, 2H), 3.54 (s, 3H).

Example 100

N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide (compound 159)

[0248] A suspension of 156 (903 mg, 3.34 mmol) in acetic anhydride (15 mL) was heated at 50°C for 1 h. Acetic anhydride was evaporated under vacuum and the solid material formed was dissolved in acetic acid (30 mL). This solution was refluxed 48h and evaporated to form another solid material, which was recrystallized from a mixture AcOEt/CHCl₃ to produce the intermediate carboxylic acid (420 mg, 43% yield). LMRS = 385.0 (M+1).

[0249] Following a procedure analogous to that described in Example 92, step 2, but substituting the carboxylic acid for 143, the title compound 159 was obtained in 49 % yield. ^1H NMR: (DMSO) δ (ppm): 9.64 (bs, 1H), 8.17 (dd, $J = 8.0, 1.6$ Hz, 1H), 7.95 (d, $J = 8.2$ Hz, 2H), 7.95 (dd, $J = 8.8, 2.5$ Hz, 1H), 7.84 (ddd, $J = 7.6, 7.0, 1.5$ Hz, 1H), 7.64 (d, $J = 7.7$ Hz, 1H), 7.53 (ddd, $J = 7.6, 7.6, 1.1$ Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 2H), 7.14 (dd, $J = 7.7, 1.1$ Hz, 1H), 6.96 (ddd, $J = 7.6, 7.6, 1.5$ Hz, 1H), 6.77 (dd, $J = 8.0, 1.4$ Hz, 1H), 6.58 (ddd, $J = 7.6, 7.6, 1.3$ Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H, overlaps with the DMSO signals).



Example 101

N-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide
(compound 163)

Step 1: 4-Methoxybenzyl-thiourea (compound 161)

[0250] To a solution of thiocarbonyl diimidazole (1.23g, 6.22 mmol, 1.5 equiv.) in dry dichloromethane (10 mL), neat alkylamine 160 (4.15 mmol, 1.0 equiv.) was added dropwise at 0°C, and the solution stirred from 0°C to 15°C during 16 h. A solution of concentrated ammonium hydroxide (3 mL, 45 mmol, 3.6 equiv.) in 1,4-dioxane (6 mL) was added at 0°C and stirred at room temperature for 7 h. The solution was diluted with ethyl acetate (250 mL), washed with brine (2 x 50 mL), dried (MgSO_4), filtered and concentrated. After purification by column chromatography (silica gel, elution 5% methanol in dichloromethane), 161 was obtained as yellow solid (700.2 mg, 3.6 mmol, 86% yield). ^1H NMR: (Acetone- d_6) δ (ppm): 7.53 (bs, 1H), 7.28 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.67 (bs, 2H), 4.67 (s, 2H), 3.77 (s, 3H). LMRS = 197.1 (M+1).

Step 2: 2-(4-Methoxybenzylamino)thiazole-5-carboxylic acid methyl ester (compound 162).

[0251] A solution of trans methyl-2-methoxyacrylate (461 mg, 3.97 mmol, 1 equiv.) in 50% 1,4-dioxane in water (4 mL) stirred at -10°C, was treated with N-bromosuccinimide (792 mg, 4.46 mmol, 1.12 equiv.), stirred at the same temperature for 1h, transferred to a flask containing the thiourea 161 (700.2 mg, 3.6 mmol) and the mixture was stirred at 80°C for 2h. After cooling down to room temperature, concentrated NH₄OH (0.8 mL) was added, stirred for 10 min and the resulting precipitated filtered and washed with water, giving 363 mg (1.3 mmol, 36% yield) of 162, plus 454 mg additional (91 % pure by HPLC) as residue from evaporation of the filtrated (ca. 77% overall yield). ¹H NMR: (Acetone-d₆) δ (ppm): 7.97 (bs, 1H), 7.72 (bs, 1H), 7.33 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.1 Hz, 2H), 4.52 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H). LMRS = 279.1 (M+1).

Step 3: N-(2-aminophenyl)-2-(4-Methoxy-benzylamino)-thiazol-5-yl-amide (compound 163)

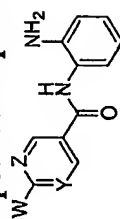
[0252] Following the procedure described in Example 1, steps 4 and 5, but substituting 162 for 6, the title compound 163 was obtained in 50% yield. ¹H-NMR (methanol-d₄), δ (ppm): 7.86 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 7.11 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 7.04 (dt, J = 8.0 Hz, 1.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 6.86 (m, 1H), 6.74 (dt, J = 7.4 Hz, 1.4 Hz, 1H), 4.85 (bs, 4H), 4.45 (s, 2H), 3.78 (s, 3H).

Examples 102-121

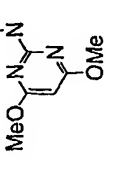
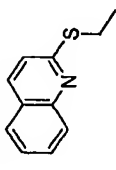
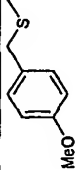
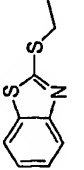
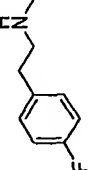
[0253] Examples 102 to 121 describe the preparation of compounds 164 to 183 using the same procedures as described for compounds 62 to 163 in Examples 47 to 101. Characterization data are presented in Tables 4a and 4b.

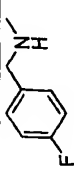
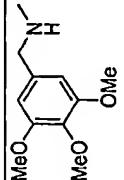
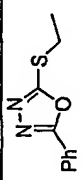
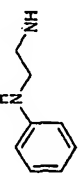
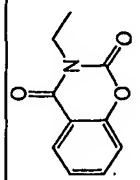
Table 4a

Characterization of Compounds Prepared in Examples 102-121

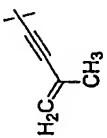
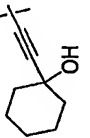
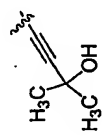

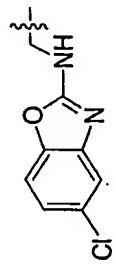
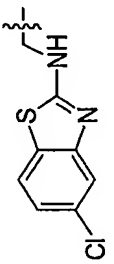


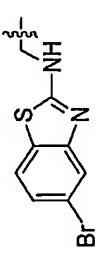
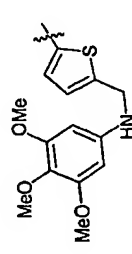
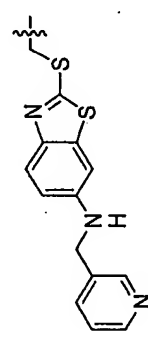
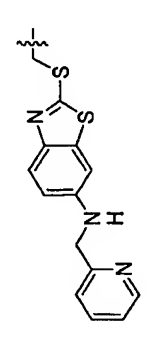
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|--|------|
| 102 | 164 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR: (Acetone-d ₆) δ (ppm): 9.09 (bs, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.00 (t, J = 6.6 Hz, 1H), 6.86 (dd, J = 8.0 Hz, 1.1 Hz, 1H), 6.67 (t, J = 8.0 Hz, 1H), 5.99 (s, 2H), 5.46 (bs, 1H), 4.64 (bs, 2H), 4.43 (s, 2H), 3.69 (s, 6H), 3.60 (s, 3H). | 11 |
| 103 | 165 | | N | CH | <i>N</i> -(2-Amino-phenyl)-6-(3-hydroxymethyl-phenyl)-nicotinamide | ¹ H NMR (20% CD ₃ OD in CDCl ₃) δ (ppm): 9.14 (d, J = 1.8 Hz, 1H), 8.33 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.93 (s, 1H), 7.82 (m, 2H), 7.50-7.40 (m, 2H), 7.22-6.45 (m, 4H), 4.69 (s, 2H). | 15 |
| 104 | 166 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(3-methoxy-phenyl)-benzamide | ¹ H NMR (CD ₃ OD) δ (ppm): 7.98 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.31-7.04 (m, 5H), 6.92-6.80 (m, 3H), 3.84 (s, 3H). | 15 |
| 105 | 167 | | CH | N | <i>N</i> -(2-amino-phenyl)-6-(4-methoxy-benzylamino)-nicotinamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.33 (s, 1H), 8.61 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 5.8 Hz, 1H), 7.24 (d, J = 8.52 Hz, 2H), 7.11 (d, J = 7.69 Hz, 1H), 6.90 (m, 3H), 6.73 (d, J = 8.0 Hz, 1H), 6.50-6.58 (m, 2H), 4.83 (s, 2H), 4.45 (d, J = 5.8 Hz, 2H), 3.70 (s, 3H). | 6 |
| 106 | 168 | | CH | N | <i>N</i> -(2-amino-phenyl)-6-[2-(4-methoxy-phenyl)-ethylamino]-nicotinamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.42 (s, 1H), 8.72 (d, J = 2.5 Hz, 1H), 7.97 (dd, J = 8.8 Hz, 2.5 Hz, 1H), 7.23 (m, 4H), 6.81-7.03 (m, 4H), 6.64 (m, 1H), 6.56 (d, J = 9.1 Hz, 1H), 4.92 (s, 2H), 3.78 (s, 3H), 3.55 (m, 2H), 2.85 (t, J = 7.3 Hz, 2H). | 6 |

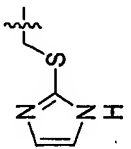

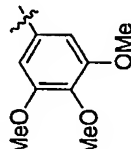
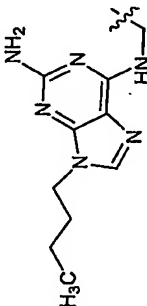
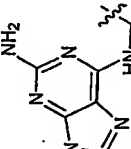
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 107 | 169 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4- [(4,6-dimethoxy- pyrimidin-2-ylamino)- methyl]-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.63 (bs, 1H), 7.95 (d, J = 7.9 Hz, 2H), 7.85-7.82 (m, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.03 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 6.63 (dt, J = 7.9 Hz, 7.7 Hz, 1H), 4.94 (bs, 2H), 4.54 (d, J = 6.0 Hz, 2H), 3.79 (bs, 6H). | 11 |
| 108 | 170 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4- (quinolin-2- ylsulfanylmethyl)- benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.62 (bs, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.00-7.89 (m, 4H), 7.79 (dd, J = 6.8 Hz, 1.3 Hz, 1H), 7.68 (d, J = 6.3 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.99 (dt, J = 7.9 Hz, 7.4 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.61 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 4.69 (s, 2H). | 11 |
| 109 | 171 |  | N | CH | <i>N</i> -(2-Amino-phenyl)-6- (4-methoxy- benzylsulfanylmethyl)- nicotinamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.06 (bs, 1H), 8.17 (dt, J = 10.9 Hz, 9.0 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.21-7.13 (m, 2H), 7.01 (dt, J = 7.6 Hz, 7.4 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 7.9 Hz, 1H), 6.62 (t, J = 7.4 Hz, 1H), 5.01 (bs, 2H), 4.47 (s, 2H), 3.76 (s, 3H). | 12 |
| 110 | 172 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4- (benzothiazol-2- ylsulfanylmethyl)- benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 8.01 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.90 (dd, J = 4.4 Hz, 0.6 Hz, 1H), 7.63 (d, J = 8.2 Hz, 2H), 7.48 (dt, J = 8.0 Hz, 0.8 Hz, 1H), 7.37 (td, J = 7.1 Hz, 1.1 Hz, 1H), 7.14 (d, J = 7.1 Hz, 1H), 6.96 (t, J = 6.3 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 6.58 (t, J = 6.6 Hz, 1H), 4.88 (s, 2H), 4.73 (s, 2H). | 11 |
| 112 | 174 |  | CH | N | <i>N</i> -(2-amino-phenyl)-6- [2-(4-fluoro-phenyl)- ethylamino]- nicotinamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.34 (s, 1H), 8.64 (d, J = 2.5 Hz, 1H), 7.89 (dd, J = 9 Hz, 2 Hz, 1H), 7.16-7.22 (m, 3H), 7.06-7.20 (m, 3H), 6.90-6.96 (m, 1H), 6.72-6.78 (m, 1H), 6.46-6.60 (m, 2H), 4.92 (s, 2H), 3.50 (m, 2H), 2.92 (m, 2H). | 6 |

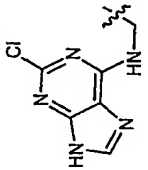
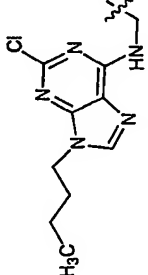
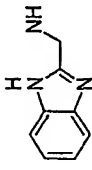
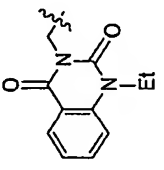
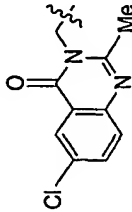
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|--|----|----|--|--|------|
| 113 | 175 |  | CH | N | <i>N</i> -(2-amino-phenyl)-6-(4-fluoro-benzylamino)-nicotinamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.34 (s, 1H), 8.61 (d, J = 2.2 Hz, 1H), 7.91 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.66 (t, J = 6 Hz, 1H), 7.32-7.37 (m, 2H), 7.08-7.38 (m, 3H), 6.93 (m, 1H), 6.74 (m, 1H), 6.52-6.58 (m, 2H), 4.84 (s, 2H), 4.51 (d, J = 6.0 Hz) | 6 |
| 114 | 176 |  | CH | N | <i>N</i> -(2-amino-phenyl)-6-(3,4,5-trimethoxy-benzylamino)-nicotinamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.34 (s, 1H), 8.63 (d, J = 2.2 Hz, 1H), 7.92 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.57 (t, J = 6 Hz, 1H), 7.10 (m, 1H), 6.93 (m, 1H), 6.74 (m, 1H), 6.66 (s, 2H), 6.56 (m, 2H), 4.84 (s, 2H), 4.45 (d, J = 6 Hz, 2H), 3.73 (s, 6H), 3.31 (s, 3H). | 6 |
| 115 | 177 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(5-phenyl-[1,3,4]oxadiazol-2-yl)sulfanylmethyl]-benzamide | ¹ H NMR: (Acetone-d ₆) δ (ppm): 9.08 (bs, 1H), 8.02 (dd, J = 7.1 Hz, 1.9 Hz, 4H), 7.69 (d, J = 8.5 Hz, 2H), 7.62-7.57 (m, 3H), 7.28 (d, J = 7.7 Hz, 1H), 7.03-6.97 (m, 1H), 6.86 (d, J = 6.6 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 4.70 (s, 2H), 4.63 (bs, 2H). | 14 |
| 116 | 178 |  | N | CH | <i>N</i> -(2-aminophenyl)-6-(2-phenylamino-ethylamino)-nicotinamide | ¹ H-NMR (CD ₃ OD- <i>d</i> 4), δ (ppm): 8.67 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 8.9 Hz, 2.5 Hz, 1H), 7.58 (m, 1H), 7.51 (m, 1H), 7.15 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.08 (m, 2H), 6.89 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.76 (dt, J = 7.7 Hz, 4.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 2H), 6.60 (m, 2H), 4.87 (bs, 4H), 3.60 (t, J = 6.3 Hz, 2H), 3.35 (t, J = 6.3 Hz, 2H). | 11 |
| 117 | 179 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(2,4-dioxo-4H-benzo[e][1,3]oxazin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.62 (s, 1H), 8.00 (dd, J = 8.2 Hz, 1.9 Hz, 1H), 7.80-7.92 (m, 3H), 7.42-7.50 (m, 4H), 7.13 (d, J = 7.1 Hz, 1H), 6.95 (ddd, J = 8.0 Hz, 1.6 Hz, 1H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (t, J = 7.7 Hz, 1H), 5.13 (s, 2H), 4.87 (bs, 2H). | 11 |

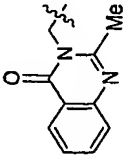
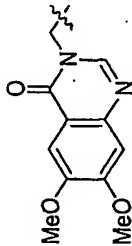
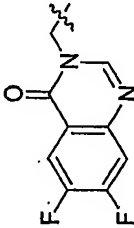
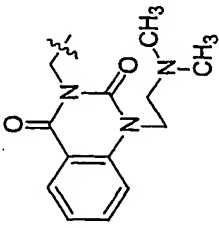
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 118 | 180 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(4-ethyl-4-methyl-2,6-dioxo-piperidin-1-ylmethyl)-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.59 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 7.4 Hz, 1H), 6.95 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.86 (bs, 2H), 2.61 (s, 2H), 2.55 (s, 2H), 1.31 (q, J = 7.7 Hz, 2H), 0.91 (s, 3H), 0.80 (t, J = 7.4 Hz, 3H). | 11 |
| 119 | 181 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (CDCl ₃) δ (ppm): 8.23 (dd, J = 7.8 Hz, 1.5 Hz, 1H), 8.01 (bs, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.71-7.65 (m, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (dt, J = 7.7, 1.5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3 Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H). | 19 |
| 120 | 182 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.66 (bs, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (t, J = 7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H). | 11 |
| 121 | 183 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(4-trifluoromethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.66 (bs, 1H), 9.07 (d, J = 5.2 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.78 (d, J = 4.7 Hz, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 7.01 (dt, J = 7.7 Hz, 7.4 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.64 (dt, J = 7.4 Hz, 7.1 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H). | 11 |

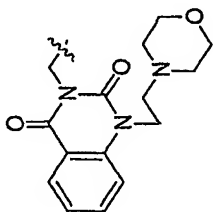
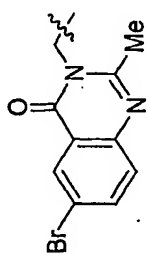
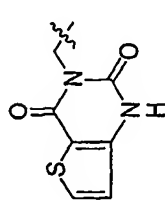
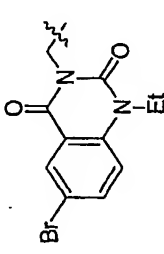
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 128 | 193 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(3-methylbut-3-en-1-ynyl)-benzamide | LRMS calc: 276.03, found: 277.2 (MH) ⁺ | 22 |
| 129 | 194 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(1-hydroxycyclohexylethynyl)-benzamide | LRMS calc: 334.4, found: 335 (MH) ⁺ | 22 |
| 130 | 195 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(3-methylbut-1-ynyl)-benzamide | LRMS calc: 294.35, found: 295.1 (MH) ⁺ | 22 |
| 131 | 196 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-phenylethynyl-benzamide | LRMS calc: 312.37, found: 313.2 (MH) ⁺ | 22 |
| 180 | 320 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(5-chloro-2-benzoxazol-2-ylamino)-methyl]-benzamide | ¹ H NMR: (Acetone-d ₆) δ (ppm): 9.67 (s, 1H), 8.85 (s, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 7.07 (dd, J = 8.8, 2.3 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.65 (t, 7.0 Hz, 1H), 4.94 (s, 2H), 4.67 (d, J = 5.3 Hz, 2H). | 35 |
| 181 | 321 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[[4-(4-chloro-phenyl)-thiazol-2-ylamino]-methyl]-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.67 (bs, 1H), 8.36 (t, J = 5.8 Hz, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.20 (s, 1H), 7.02 (t, J = 8.5 Hz, 1H), 6.83 (d, J = 7.7 Hz, 1H), 6.65 (t, J = 7.1 Hz, 1H), 4.92 (bs, 2H), 4.65 (d, J = 5.8 Hz, 2H). | 35 |

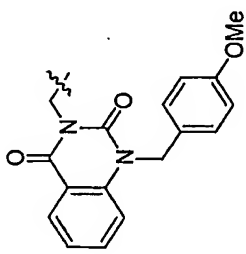
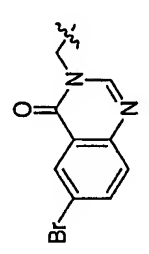
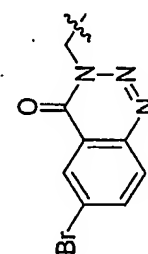
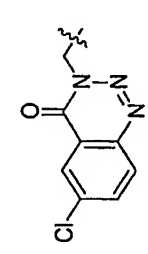
| Ex. | Cpd. | W | Y | Z | Name | Characterization | Schm |
|-----|------|---|----|----|---|---|--------|
| 182 | 322 |  | CH | CH | N-(2-Amino-phenyl)-4-[(5-bromo-benzothiazol-2-ylamino)-methyl]-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 6.97 (s, 1H), 8.78 (bs, 1H), 8.01 (d, J = 8.8 Hz, 2H), 8.00 (s, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.43-7.35 (m, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.0 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 7.6 Hz, 1H), 4.94 (s, 2H), 7.74 (d, J = 5.9 Hz, 2H). | 33, 34 |
| 183 | 323 |  | CH | CH | N-(2-Amino-phenyl)-4-{5-[(3,4,5-trimethoxy-phenylamino)-methyl]-thiophen-2-ylmethyl}-benzamide | L RMS calc: 489.58, found: 490 (MH) ⁺ | 21 |
| 184 | 325 |  | CH | CH | N-(2-Amino-phenyl)-4-{6-[(pyridin-3-ylmethyl)-amino]-benzothiazol-2-ylsulfanylmethyl}-benzamide | ¹ H NMR: (Acetone-d ₆) δ (ppm): 8.65 (d, J = 1.4 Hz, 1H), 8.44 (dd, J = 4.7, 3.0 Hz, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.81-7.77 (m, 1H), 7.63 (m, 3H), 7.33-7.26 (m, 2H), 7.09 (d, J = 2.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.91 (dd, J = 8.8, 2.5 Hz, 1H), 6.86 (dd, J = 8.0, 1.4 Hz, 1H), 6.69-6.64 (m, 1H), 4.64 (s, 2H), 4.47 (s, 2H). | 11 |
| 185 | 326 |  | CH | CH | N-(2-Amino-phenyl)-4-{6-[(pyridin-2-ylmethyl)-amino]-benzothiazol-2-ylsulfanylmethyl}-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.59 (s, 1H), 8.52-8.51 (m, 1H), 7.89 (d, J = 8.24 Hz, 2H), 7.71 (td, J = 7.7, 1.9 Hz, 1H), 7.59-7.53 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.12 (d, J = 6.9 Hz, 1H), 6.98-6.96 (m, 1H), 6.93 (d, J = 7.4 Hz, 1H), 6.81 (dd, J = 9.1, 2.5 Hz, 1H), 6.76-6.73 (m, 1H), 6.67 (t, J = 5.8 Hz, 1H), 6.56 (t, J = 7.4 Hz, 1H), 4.87 (s, 1H), 4.58 (s, 2H), 4.38 (d, J = 6.3 Hz, 2H). | 11, 34 |

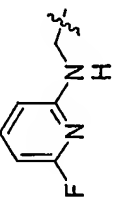
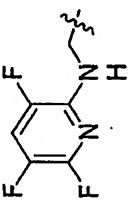
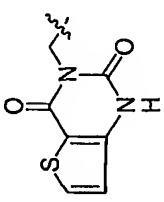
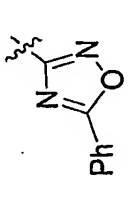
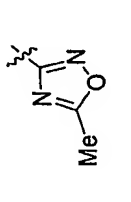
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 186 | 327 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(1H-imidazol-2-yl)sulfanylmethylbenzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 12.23 (bs, 1H), 9.59 (s, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.14-7.12 (m, 2H), 6.94-6.92 (m, 2H), 6.76 (d, J = 6.6 Hz, 1H), 6.57 (t, J = 7.4 Hz, 1H), 4.87 (s, 2H), 4.29 (s, 2H). | 14 |
| 187 | 328 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-morpholin-4-ylmethylbenzamide | ¹ H NMR: (CD ₃ OD) δ (ppm): 8.03 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 7.9 Hz, 2H), 7.26 (d, J = 7.0 Hz, 1H), 7.16 (t, J = 6.6 Hz, 1H), 6.98 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.5 Hz, 1H), 3.78 (t, J = 4.4 Hz, 4H), 3.68 (s, 2H), 2.57-2.54 (m, 4H). | 37 |
| 188 | 329 |  | CH | CH | 3',4',5'-Trimethoxybiphenyl-4-carboxylic acid (2-amino-phenyl)-amide | ¹ H NMR: (CD ₃ OD) δ (ppm): 8.14 (d, J = 7.9 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 7.17 (t, J = 7.0 Hz, 1H), 7.04 (s, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 4.95 (s, 6H), 4.01 (s, 3H). | 37 |
| 189 | 330 |  | CH | CH | 4-[(2-Amino-9-butyl-9H-purin-6-ylamino)-methyl]- <i>N</i> -(2-amino-phenyl)-benzamide | ¹ H NMR: (DMSO-d ₆) δ (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.7 Hz, 2H), 7.95 (bs, 2H), 7.78 (s, 1H), 7.52 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (dd, J = 7.3, 8.0 Hz, 1H), 6.8 (d, J = 8.0 Hz, 1H), 6.65 (dd, J = 7.3, 7.7 Hz, 1H), 5.91 (s, 2H), 4.94 (bs, 2H), 4.77 (bs, 2H), 4.01 (t, J = 7.1 Hz, 1H), 1.78 (m, 2H), 1.3 (m, 2H), 0.95 (t, J = 7.4, Hz, 1H). | 39 |
| 190 | 331 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(2-amino-9H-purin-6-ylamino)-methyl]-benzamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 10.16 (s, 1H), 9.60 (br, 1H), 8.24 (s, 1H), 8.08 (d, J = 8.0 Hz, 2H), 7.62 (m, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.20 (m, 2H), 7.08 (m, 1H), 4.90 (m, 2H), 4.6 (br, 4H). | 39 |

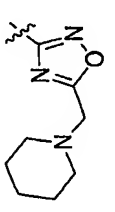
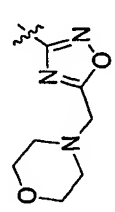
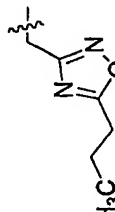
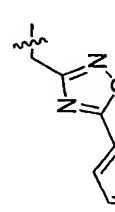
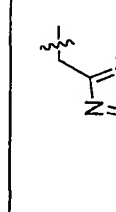
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|------|
| 191 | 332 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(2-chloro-9 <i>H</i> -purin-6-ylamino)-methyl]-benzamide | ¹ H NMR (DMSO- <i>d</i> ₆) δ (ppm): 9.67 (m, 1H), 8.80 (m, 1H), 8.24 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 7.8 Hz, 1H), 7.02 (dd, J = 6.3, 7.8 Hz, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.70 (dd, J = 6.3, 8.1 Hz, 1H), 4.94 (br, 2H), 4.77 (br, 2H) | 39 |
| 192 | 333 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(9-butyl-2-chloro-9 <i>H</i> -purin-6-ylamino)-methyl]-benzamide | ¹ H NMR (DMSO- <i>d</i> ₆) δ (ppm): 9.60 (s, 1H), 8.72 (br, 1H), 8.21 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 6.96 (dd, J = 6.7, 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.58 (dd, J = 6.7, 8.0 Hz, 2H), 4.88 (s, 1H), 4.71 (m, 2H), 4.11 (m, 2H), 1.76 (m, 2H), 1.25 (m, 2H), 0.89 (t, J = 7.1 Hz, 3H) | 39 |
| 193 | 334 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(1 <i>H</i> -benzimidazol-2-ylmethyl)-amino]-benzamide | ¹ H NMR: (DMSO- <i>d</i> ₆) δ (ppm): 12.39 (bs, 1H), 9.32 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.56 (bs, 1H), 7.21-7.17 (m, 3H), 6.99-6.97 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.63 (t, J = 7.0 Hz, 1H), 4.85 (s, 2H), 4.62 (d, J = 5.3 Hz, 2H) | 11 |
| 194 | 335 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2 <i>H</i> -quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (CDCl ₃) δ (ppm): 8.23 (dd, J = 7.8, 1.5 Hz, 1H), 8.01 (bs, 1H), 7.80 (d, J = 8.0 Hz, 2H), 7.71-7.65 (m, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.27-7.20 (m, 3H), 7.05 (td, J = 7.7, 1.5 Hz, 1H), 6.81-6.77 (m, 2H), 5.29 (bs, 2H), 4.18 (q, J = 7.3 Hz, 2H), 3.86 (bs, 2H), 1.33 (t, J = 7.1 Hz, 3H). MS: (calc.) 414.2; (obt.) 415.3 (MH) ⁺ | 19 |
| 195 | 336 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(6-chloro-2-methyl-4-oxo-4 <i>H</i> -quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.69 (bs, 1H, NH), 8.71 (s, 1H), 8.16 (d, J = 2.5 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.81 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 7.1 Hz, 1H), 7.02 (td, J = 7.6, 1.5 Hz, 1H), 6.82 (dd, J = 8.0, 1.4 Hz, 1H), 6.64 (td, J = 7.6, 1.4 Hz, 1H), 5.34 (s, 2H), 4.94 (bs, 2H). MS: (calc.) 404.1; (obt.) 405.0 (MH) ⁺ | 19 |

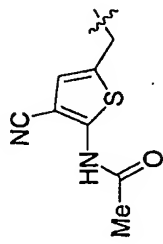
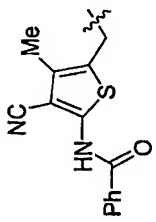
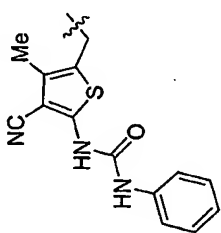
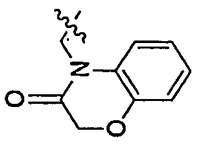
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|------|
| 196 | 337 |  | CH | CH | N-(2-Amino-phenyl)-4-(2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.64 (bs, 1H), 8.17 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.95 (dd, J = 8.8, 2.5 Hz, 1H), 7.84 (ddd, J = 7.6, 7.0, 1.5 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.53 (ddd, J = 7.6, 7.6, 1.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.14 (dd, J = 7.7, 1.1 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.58 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 5.46 (s, 2H), 4.89 (bs, 2H) 2.5 (s, 3H). MS: (calc.) 384.2; (obt.) 385.0 (MH) ⁺ | 19 |
| 197 | 338 |  | CH | CH | N-(2-Amino-phenyl)-4-(6,7-dimethoxy-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.62 (bs, 1H), 8.50 (s, 1H), 8.41 (d, J = 8.2 Hz, 2H), 7.47 (s, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.17 (s, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.96 (ddd, J = 7.7, 7.7, 1.1 Hz, 1H), 6.76 (d, J = 6.9 Hz, 1H), 6.58 (dd, J = 6.9, 6.9 Hz, 1H), 5.26 (s, 2H), 4.88 (bs, 2H), 3.91 (s, 3H), 3.87 (s, 3H). MS: (calc.) 430.2; (obt.) 431.1 (MH) ⁺ | 19 |
| 198 | 339 |  | CH | CH | N-(2-Amino-phenyl)-4-(6,7-difluoro-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.66 (bs, 1H), 8.69 (s, 1H), 8.07 (dd, J = 8.8, 10.4 Hz, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.82 (dd, J = 14.3, 11.3 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.76 (dd, J = 8.1, 1.2 Hz, 1), 6.58 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.28 (s, 2H), 4.89 (bs, 2H). MS: (calc.) 406.1; (obt.) 407.0 (MH) ⁺ | 19 |
| 199 | 340 |  | CH | CH | N-(2-Amino-phenyl)-4-[1-(2-dimethylaminoethyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 7.8, 1.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.81 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.6, 7.6 Hz, 1H), 7.14 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 7.8, 1.2 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.22 (s, 2H), 4.88 (bs, 2H), 4.24 (t, J = 7.1 Hz, 2H), 2.5 (m, 2H) 2.22 (s, 6H). MS: (calc.) 457.2; (obt.) 458.1 (MH) ⁺ | 19 |

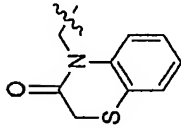
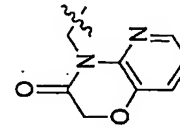
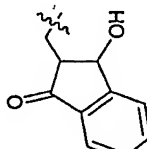
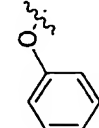
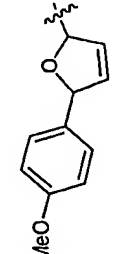
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|--|------|
| 200 | 341 |  | CH | CH | N-(2-Amino-phenyl)-4-(1-(2-morpholin-4-yl-ethyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.09 (dd, J = 8.0, 1.6 Hz, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.81 (ddd, J = 7.8, 7.8, 1.6 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 8.2 Hz, 2H), 7.32 (dd, J = 7.4, 7.4 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.22 (s, 2H), 4.87 (bs, 2H), 4.28 (t, J = 6.7 Hz, 2H), 3.50 (t, J = 4.5 Hz, 4H), 2.58 (t, J = 6.7 Hz, 2H), 2.47-2.44 (m, 4H). MS: (calc.) 499.2; (obt.) 500.3 (MH) ⁺ . | 19 |
| 201 | 342 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-2-methyl-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.65 (bs, 1H), 8.25 (d, J = 2.5 Hz, 1H), 7.99 (ddd, J = 8.5, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.14 (d, J = 7.4 Hz, 1H), 6.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.45 (s, 2H), 4.88 (bs, 2H). MS: (calc.) 462.1; (obt.) 463.1 (MH) ⁺ . | 19 |
| 202 | 343 |  | CH | CH | N-(2-Amino-phenyl)-4-(2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 5.2, 0.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 5.12 (s, 2H), 4.88 (bs, 2H). MS: (calc.) 392.1; (obt.) 393.0 (MH) ⁺ . | 43 |
| 203 | 344 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-1-ethyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.15 (d, J = 2.5 Hz, 1H), 7.95 (dd, J = 9.1, 4.9 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 9.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.1, 1.5 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.20 (s, 2H), 4.88 (bs, 2H), 4.14 (q, J = 7.0, 2H), 1.21 (t, J = 7.0, 3H). MS: (calc.) 492.1; (obt.) 493.0 (MH) ⁺ . | 19 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|------|
| 204 | 345 |  | CH | CH | N-(2-Amino-phenyl)-4-[1-(4-methoxy-benzyl)-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.62 (bs, 1H), 8.10 (dd, J = 7.7, 1.6 Hz, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.71 (ddd, J = 7.9, 7.9, 1.5 Hz, 1H), 7.46 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 7.4 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 6.6 Hz, 1H), 6.96 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.33 (s, 2H), 5.28 (s, 2H), 4.89 (bs, 2H), 3.71 (s, 3H). MS: (calc.) 506.2; (obt.) 507.1 (MH) ⁺ . | 19 |
| 205 | 346 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-4-oxo-4H-quinazolin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.66 (s, 1H), 8.24 (d, J = 2.5 Hz, 1H), 8.00 (dd, J = 8.7, 2.3 Hz, 1H), 7.95 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.28 (s, 2H), 4.87 (bs, 2H). MS: (calc.) 448.0; (obt.) 449.0 (MH) ⁺ . | 19 |
| 206 | 347 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-bromo-4-oxo-4H-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.63 (bs, 1H), 8.38 (d, J = 1.9 Hz, 1H), 8.28 (dd, J = 8.8, 2.2 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 6.9 Hz, 1H), 7.96 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.59 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 5.67 (s, 2H), 4.87 (bs, 2H). MS: (calc.) 449.0; (obt.) 450.0 (MH) ⁺ . | 19 |
| 207 | 348 |  | CH | CH | N-(2-Amino-phenyl)-4-(6-chloro-4-oxo-4H-benzo[d][1,2,3]triazin-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.63 (bs, 1H), 8.30-8.24 (m, 2H), 8.15 (ddd, J = 8.6, 2.5, 0.8 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.0 Hz, 1H), 7.96 (dd, J = 7.4, 7.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.67 (s, 2H), 4.88 (bs, 2H). MS: (calc.) 405.1; (obt.) 406.0 (MH) ⁺ . | 19 |

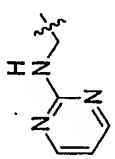
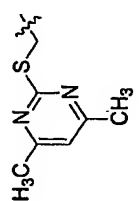
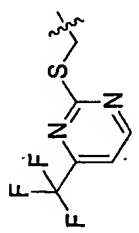
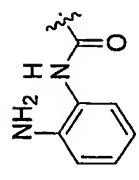
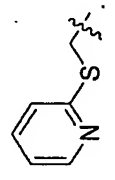
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 208 | 349 |  | CH | CH | N-(2-Amino-4-[(3-fluoro-2-pyridinyl)amino]methyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.07 (bs, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.64-7.44 (m, 3H), 7.33 (dd, J = 7.8, 1.5 Hz, 1H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.78 (bs, 1H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 6.48 (dd, J = 8.1, 2.6 Hz, 1H), 6.16 (dd, J = 7.7, 2.5 Hz, 1H), 4.76-4.55 (m, 4H). HRMS (calc.): 336.1386, (found): 336.1389. | 11 |
| 209 | 350 |  | CH | CH | N-(2-Amino-4-[(3,4,5-trifluoro-2-pyridinyl)amino]methyl)-benzamide | ¹ H NMR (acetone-d ₆) δ (ppm): 9.06 (bs, 1H), AB system (δ _A = 8.02, δ _B = 7.56, J = 8.3 Hz, 4H), 7.74-7.65 (m, 1H), 7.33 (d, J = 8.0, 1H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.96-6.83 (m, 2H), 6.71 (td, J = 7.6, 1.4 Hz, 1H), 4.74 (d, J = 6.3 Hz, 2H), 4.65 (bs, 2H). | 11 |
| 210 | 351 |  | CH | CH | N-(2-Amino-4-(2,4-dioxo-1,4-dihydro-2H-thienol[3,2-d]pyrimidin-3-yl)methyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.10 (dd, J = 5.2, 0.5 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 7.1 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (dd, J = 8.0, 1.1 Hz, 1H), 6.58 (dd, J = 7.1, 7.1 Hz, 1H), 5.12 (s, 2H), 4.88 (bs, 2H). MS: (calc.) 392.1; (obt.) 393.0 (MH) ⁺ . | 43 |
| 211 | 352 |  | CH | CH | N-(2-Amino-4-(5-phenyl-[1,2,4]oxadiazol-3-yl)methyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.85 (bs, 1H), 8.24-8.19 (m, 6H), 7.79-7.66 (m, 3H), 7.20 (d, J = 7.5 Hz, 1H), 7.00 (dd, J = 7.3, 7.3 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.3, 7.3 Hz, 1H), 4.96 (bs, 2H). MS: (calc.) 356.1; (obt.) 357.0 (MH) ⁺ . | 50 |
| 212 | 353 |  | CH | CH | N-(2-Amino-4-(5-methyl-[1,2,4]oxadiazol-3-yl)methyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.81 (bs, 1H), 8.17-8.11 (m, 4H), 7.18 (d, J = 7.9 Hz, 1H), 6.99 (dd, J = 7.7, 7.7 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.61 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (bs, 2H), 2.70 (s, 3H). MS: (calc.) 294.1; (obt.) 295.0 (MH) ⁺ . | 50 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 213 | 354 |  | CH | CH | N-(2-Amino-phenyl)-4-(5-piperidin-1-ylmethyl-[1,2,4]oxadiazol-3-yl)-benzamide | ¹ H NMR: (acetone) δ (ppm): 9.29 (bs, 1H), 8.21 (m, 4H), 7.31 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.68 (bs, 2H), 3.94 (s, 2H), 2.58 (t, J = 5.1 Hz), 1.63-1.55 (m, 4H), 1.47-1.43 (m, 2H). MS (Calc) 377.2; (Obt.) 378.3 (MH) ⁺ | 50 |
| 214 | 355 |  | CH | CH | N-(2-Amino-phenyl)-4-(5-morpholin-4-ylmethyl-[1,2,4]oxadiazol-3-yl)-benzamide | ¹ H NMR: (acetone) δ (ppm): 9.28 (bs, 1H), 8.21 (m, 4H), 7.31 (d, J = 8.1 Hz, 1H), 7.03 (dd, J = 7.0, 7.0 Hz, 1H), 6.88 (d, J = 7.3 Hz, 1H), 6.69 (dd, J = 7.3, 7.3 Hz, 1H), 4.67 (bs, 2H), 4.01 (s, 2H), 3.66 (t, J = 4.8 Hz), 2.65 (t, J = 4.4 Hz). MS: (Calc.) 379.2; (Obt.): 380.2 (MH) ⁺ | 50 |
| 215 | 356 |  | CH | CH | N-(2-Amino-phenyl)-4-(5-propyl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.62 (s, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.88 (s, 2H), 4.16 (s, 2H), 2.87 (t, 7.0, 2H), 1.72 (q, J = 7.5 Hz, 2H), 0.92 (t, J = 7.0 Hz, 3H). (MH) ⁺ : 337.2. | 50 |
| 216 | 357 |  | CH | CH | N-(2-Amino-phenyl)-4-(5-pyridin-3-yl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.64 (s, 1H), 9.24 d, J = 1.8 Hz, 1H; 8.86 (dd, J = 1.3 Hz, J = 4.8 Hz, 1H), 8.45 (dd, J = 1.8 Hz, J = 6.2 Hz, 1H), 7.96 (d, J = 7.9 Hz, 2H), 7.66 (dd, J = 4.8 Hz, J = 7.9 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 4.89 (s, 2H), 4.31 (s, 2H). (MH) ⁺ : 372.3. | 50 |
| 217 | 358 |  | CH | CH | N-(2-Amino-phenyl)-4-(5-pyridin-4-yl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.63 (s, 1H), 8.87 (d, J = 6.2 Hz, 2H); 7.95-8.02 (m, 3H), 7.50 (d, J = 7.9 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.33 (s, 2H). (MH) ⁺ : 372.3. | 50 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|--|----|----|---|---|------|
| 218 | 359 |  | CH | CH | 4-(5-Acetylamino-4-cyano-thiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide | ¹ H NMR (DMSO) δ (ppm): 11.62 (s, 1H), 9.60 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 7.3 Hz, 1H), 7.15 (d, J = 7.3 Hz, 1H), 6.98-6.94 (m, 2H), 6.77 (d, J = 7.3 Hz, 1H), 6.591 (dd, J = 7.7, 7.7 Hz, 1H), 4.89 (bs, 2H), 4.13 (s, 2H), 2.17 (s, 3H). LRMS: 390.1 (calc) 391.2 (found). | 49 |
| 219 | 360 |  | CH | CH | 4-(5-Benzoylamino-4-cyano-3-methylthiophen-2-ylmethyl)-N-(2-amino-phenyl)-benzamide | ¹ H NMR (DMSO) δ (ppm): 11.77 (s, 1H), 9.61 (s, 1H), 7.93 (d, J = 7.0 Hz, 4H), 7.52-7.63 (m, 3H), 7.38 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.89 (s, 2H), 4.15 (s, 2H), 2.24 (s, 3H). (MH) ⁺ : 467.0 | 49 |
| 220 | 361 |  | CH | CH | N-(2-Amino-phenyl)-4-[4-cyano-3-methyl-5-(3-phenyl-ureido)-thiophen-2-ylmethyl]-benzamide | ¹ H NMR (DMSO) δ (ppm): 10.12 (s, 1H), 9.61 (s, 1H), 9.21 (s, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.27-7.43 (m, 6H), 7.16 (d, J = 7.6 Hz, 1H), 6.93-7.05 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H), 4.08 (s, 2H), 2.19 (s, 3H). (MH) ⁺ : 482.4 | 49 |
| 221 | 362 |  | CH | CH | N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydrobenzo[1,4]oxazin-4-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.60 (s, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 6.9 Hz, 1H), 6.92-7.04 (m, 5H), 6.75 (dd, J = 8.1 Hz, 1.1 Hz, 1H), 6.57 (td, J = 7.4 Hz, 1.4 Hz, 1H), 5.24 (s, 2H), 4.88 (bs, 2H); 4.82 (s, 2H). (MH) ⁺ : 374.1 | 11 |

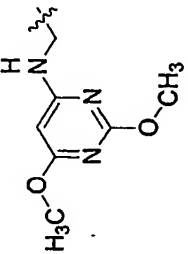
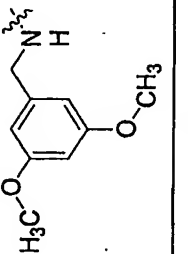
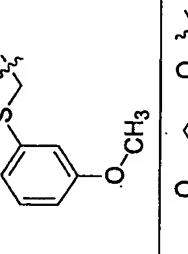
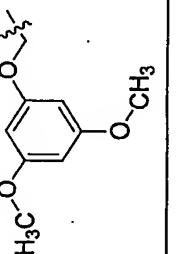
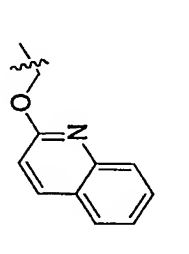
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|------|
| 222 | 363 |  | CH | CH | N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-benzo[1,4]thiazin-4-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.58 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.42 (dd, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.19-7.11 (m, 3H), 7.04-6.92 (m, 2H), 6.75 (dd, J = 8.0 Hz, 1.4 Hz, 1H), 6.57 (td, J = 8.0 Hz, 1.6 Hz, 1H), 5.31 (s, 2H); 4.88 (bs, 2H); 3.70 (s, 2H). (MH) ⁺ : 390.1 | 11 |
| 223 | 364 |  | CH | CH | N-(2-Amino-phenyl)-4-(3-oxo-2,3-dihydro-pyrido[3,2-b][1,4]oxazin-4-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.57 (bs, 1H), 7.98 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.45-7.40 (m, 3H), 7.15 (d, J = 8.2 Hz, 1H), 7.09-7.05 (m, 1H), 6.96 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 6.58 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 5.31 (s, 2H), 4.90 (bs, 2H), 4.87 (s, 2H). (MH) ⁺ : 375.1 | 11 |
| 224 | 365 |  | CH | CH | N-(2-Amino-phenyl)-4-(1-hydroxy-3-oxo-indan-2-ylmethyl)-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.67 (s, 1H); 7.98 (d, J = 8.2 Hz, 2H), 7.73-7.84 (m, 3H), 7.53-7.62 (m, 3H), 7.24 (d, J = 7.6 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 5.68 (d, J = 7.0 Hz, 1H), 5.27 (t, J = 6.4 Hz, 1H), 4.95 (s, 2H), 3.21-3.30 (m, 1H), 3.11-3.13 (m, 2H). (MH) ⁺ : 373.1 | 46 |
| 225 | 366 |  | CH | CH | N-(2-Amino-phenyl)-4-phenoxy-benzamide | ¹ H NMR: (DMSO) δ (ppm): 9.61 (s, 1H); 8.01 (d, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.06-7.24 (m, 6H), 6.97 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.59 (t, J = 7.6 Hz, 1H), 4.88 (s, 2H). (MH) ⁺ : 305.0 | 1 |
| 226 | 367 |  | CH | CH | N-(2-Amino-phenyl)-4-[5-(4-methoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzamide | ¹ H NMR (CDCl ₃) δ (ppm): 8.77 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.38-6.98 (m, 6H), 6.91 (d, J = 8.4 Hz, 2H), 6.09-5.98 (m, 4H), 3.81 (s, 3H). | 52 |

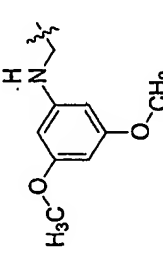
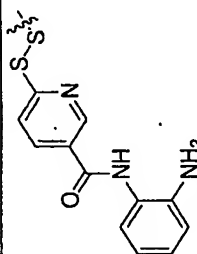
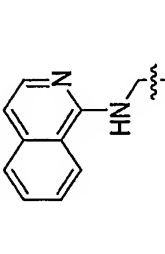
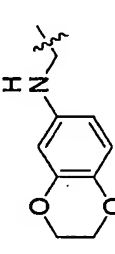
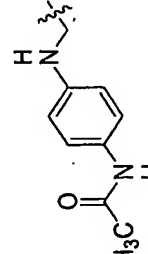
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 230 | 371 | | CH | CH | <i>N</i> -(2-Amino-4-[1,3-bis(methoxy)phenoxy]-3-(4-dimethoxyphenyl)phenyl)-ureidomethylbenzamide | ¹ H NMR (DMSO-d ₆): δ 10.08 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.70 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39-7.33 (m, 1H), 7.30-6.90 (m, 7H), 6.87 (dd, J = 2.2, 8.35 Hz, 1H), 6.78 (dd, J = 2.2, 8.35 Hz, 1H), 5.01 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H). | 57 |
| 231 | 372 | | CH | CH | <i>N</i> -(2-Amino-4-[3-(4-chlorophenyl)-1-(3,4-dimethoxyphenyl)ureidomethyl]phenyl)-benzamide | ¹ H NMR (CDCl ₃): δ 8.02 (brs, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.5 Hz, 2H), 7.42-7.24 (m, 6H), 7.16 (t, J = 7.5 Hz, 1H), 6.91 (brd, J = 5.71 Hz, 3H), 6.75 (brd, J = 8.3 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 4.99 (s, 1H), 3.97 (s, 3H), 3.86 (s, 3H). | 57 |
| 232 | 373 | | CH | CH | <i>N</i> -(2-Amino-4-[1-(3,4-dimethoxyphenyl)-3-phenylureidomethyl]phenyl)-benzamide | ¹ H NMR (DMSO-d ₆): δ 10.10 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.88 (s, 1H), 7.80-7.72 (m, 1H), 7.50 (dd, J = 7.0, 5.7 Hz, 4H), 7.37 (d, J = 7.9 Hz, 1H), 7.30-6.94 (m, 7H), 6.78 (d, J = 6.6 Hz, 1H), 5.03 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). | 57 |
| 233 | 374 | | CH | CH | <i>N</i> -(2-Amino-4-[1-(3,4-dimethoxyphenoxy)-3-(4-phenoxyphenyl)ureidomethyl]phenyl)-benzamide | ¹ H NMR (CDCl ₃): δ 8.02 (brs, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 8.35 Hz, 2H), 7.43-7.32 (m, 5H), 7.10-7.30 (2m, 5H), 7.19-7.10 (m, 2H), 7.01 (dd, J = 8.35, 2.2 Hz, 3H), 6.94 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.8, 2.2 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 6.34 (s, 2H), 5.02 (s, 2H), 3.98 (s, 3H), 3.87 (s, 3H). | 57 |
| 234 | 375 | | CH | CH | Biphényl-4,4'-dicarboxylic acid bis-[(2-amino-phenyl)-amide] | ¹ H NMR (CD ₃ OD) δ (ppm): 9.80 (bs, 2H), 8.16 (d, J = 7.9 Hz, 4H), 7.96 (d, J = 7.9 Hz, 4H), 7.23 (d, J = 7.4 Hz, 2H), 7.03 (dd, J = 6.9, 7.4 Hz, 2H), 6.84 (d, J = 8.2 Hz, 2H), 6.66 (dd, J = 6.9, 7.7 Hz, 2H), 5.06 (bs, 4H). | 15 |

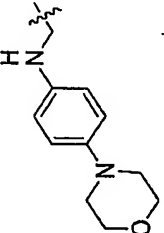
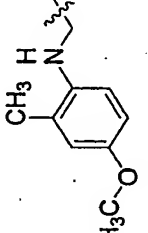
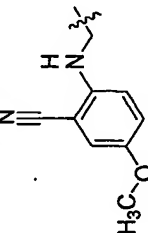
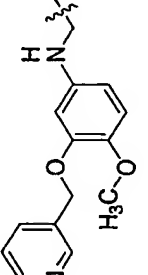
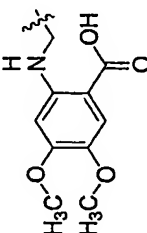
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 236 | 377 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(pyrimidin-2-ylaminomethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.6 (bs, 1H), 8.32 (d, J=4.9 Hz, 2H), 7.97 (dt, J=7.9, 9.9 Hz, 2H), 7.85-7.83 (m, 1H), 7.47, (d, J=8.2 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.01 (dt, J=7.4, 7.7 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.66-6.62 (m, 1H), 4.98 (bs, 2H), 4.61 (d, 2H). | 13 |
| 237 | 378 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(4,6-dimethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.61 (d, J=7.9 Hz, 2H), 7.21 (d, J=7.9 Hz, 1H), 7.04-6.99 (m, 2H), 6.82 (d, J=7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 4.49 (s, 2H), 2.42 (s, 6H). | 11 |
| 238 | 379 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(4-trifluoromethyl-pyrimidin-2-ylsulfanylmethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 9.07 (d, J=5.2 Hz, 1H), 7.97 (d, J=7.4 Hz, 2H), 7.78 (d, J=4.7 Hz, 1H), 7.63 (d, J=7.4 Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.01 (dt, J=7.4, 7.7 Hz, 1H), 6.81 (d, J=8.2 Hz, 1H), 6.64 (dt, J=7.1, 7.4 Hz, 1H), 4.94 (bs, 2H), 4.57 (s, 2H). | 11 |
| 239 | 380 |  | N | CH | Pyridine-2,5-dicarboxylic acid bis-[(2-amino-phenyl)-amide] | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 10.23 (bs, 1H), 10.04 (bs, 1H), 9.30 (s, 1H), 8.62 (dd, J=1.8, 8.0 Hz, 1H), 8.30 (d, J=8.1 Hz, 1H), 7.55 (d, J=7.4 Hz, 1H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=7.0, 14.0 Hz, 2H), 6.90-6.83 (m, 2H), 6.74-6.63 (m, 2H), 5.11 (bs, 4H). | 1 |
| 240 | 381 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(pyridin-2-ylsulfanylmethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 8.52 (bs, 1H), 7.96 (d, J=7.4 Hz, 2H), 7.69 (d, J=5.8 Hz, 1H), 7.59 (d, J=7.4 Hz, 2H), 7.38 (d, J=7.7 Hz, 1H), 7.19 (bs, 2H), 7.00 (d, J=6.9 Hz, 1H), 6.83 (d, J=6.9 Hz, 1H), 6.64 (dd, J=6.7, 7.2 Hz, 1H), 4.94 (bs, 2H), 4.55 (b+s, 2H). | 11 |

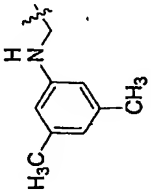
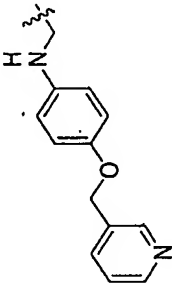
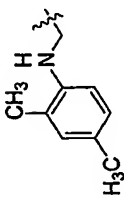
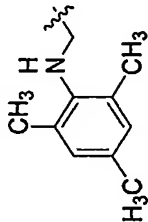
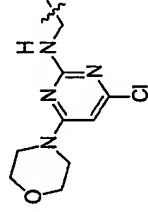
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 241 | 382 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(4,6-dimethylpyrimidin-2-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.65 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.57 (d, J=6.3 Hz, 1H), 7.47 (d, J=7.7 Hz, 2H), 7.21 (d, J=7.4 Hz, 1H), 7.00 (d, J=5.8 Hz, 1H), 6.59 (d, J=6.6 Hz, 1H), 6.64 (dd, J=6.0, 7.4 Hz, 1H), 5.01 (s, 2H), 4.61 (d, J=6.0 Hz, 2H), 2.24 (s, 6H). | 33 |
| 242 | 383 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(4,6-dimethylpyridin-2-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.50 (d, J=8.2 Hz, 2H), 7.96 (d, J=7.9 Hz, 1H), 7.01 (dd, J=7.7, 7.4 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.33 (s, 1H), 6.25 (s, 1H), 4.58 (d, J=4.4 Hz, 2H), 2.28 (s, 3H), 2.17 (s, 3H). | 33 |
| 243 | 384 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(4,6-dimethylpyrimidin-2-ylloxymethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.58 (bs, 1H), 7.88 (d, J=5.8 Hz, 2H), 7.46 (d, J=8.2 Hz, 2H), 6.90-6.81 (m, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.50 (t, J=7.4 Hz, 1H), 6.40-6.38 (m, 1H), 6.29-6.26 (m, 1H), 5.33 (s, 2H), 2.25 (s, 6H). | 11 |
| 244 | 385 | | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(6-methoxypyrimidin-2-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.64 (bs, 1H), 8.21 (bs, 1H), 7.95 (d, J=7.96 Hz, 2H), 7.83 (d, J=5.8 Hz, 1H), 7.44 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.7 Hz, 1H), 7.00 (dd, J=7.4, 7.7 Hz, 1H), 6.80 (d, J=7.9 Hz, 1H), 6.64 (d, J=7.1 Hz, 1H), 4.96 (bs, 2H), 4.58 (bs, 2H), 3.81 (s, 3H). | 33 |
| 245 | 386 | | CH | CH | 4-[(6-Acetylbenzo[1,3]dioxol-5-ylamino)-methyl]-N-(2-amino-phenyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.79 (bs, 1H), 7.99 (d, J=8.5 Hz, 2H), 7.48 (d, J=7.96 Hz, 2H), 7.39 (bs, 1H), 7.21 (d, J=7.4 Hz, 1H), 7.02 (dd, J=7.1, 7.7 Hz, 1H), 6.83 (d, J=7.7 Hz, 1H), 6.64 (t, J=7.4 Hz, 1H), 6.36 (bs, 1H), 6.00 (d, J=2.2 Hz, 2H), 4.59 (bs, 2H), 2.52 (bs, 3H). | 33 |

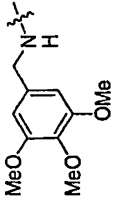
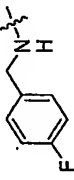
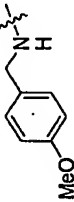
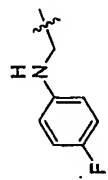
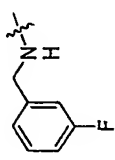
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|------|
| 246 | 387 | | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-methoxy-pyrimidin-2-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.47 (bs, 2H), 7.39 (bs, 1H), 7.19 (d, J=7.4 Hz, 1H), 7.00 (dd, J=6.9, 7.4 Hz, 1H), 6.81 (d, J=7.1 Hz, 1H), 6.63 (dd, J=7.7, 6.8 Hz, 1H), 6.10 (bs, 1H), 4.56 (d, J=6.0 Hz, 2H), 3.83 (s, 3H). | 33 |
| 247 | 388 | | CH | CH | N-(2-Amino-phenyl)-4-[(2,6-dimethoxy-pyridin-3-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.63 (bs, 1H), 7.94 (d, J=6.9 Hz, 2H), 7.47 (d, J=6.59 Hz, 2H), 7.15 (d, J=7.9 Hz, 1H), 6.99 (dd, J=5.7, 7.4 Hz, 1H), 6.80 (d, J=7.8 Hz, 1H), 6.71 (d, J=6.6 Hz, 1H), 6.62 (dd, J=7.7, 7.1 Hz, 1H), 6.15 (d, J=8.2 Hz, 1H), 4.96 (bs, 2H), 4.38 (bs, 2H), 3.94 (s, 3H), 3.75 (s, 3H). | 33 |
| 248 | 389 | | CH | CH | N-(2-Amino-phenyl)-4-[(1H-benzimidazol-2-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 10.9 (bs, 1H), 9.64 (bs, 1H), 7.99 (bs, 2H), 7.55 (bs, 2H), 7.21-7.17 (m, 3H), 7.14-6.81 (m, 4H), 6.64 (d, J=6.0 Hz, 1H), 4.92 (bs, 2H), 4.65 (bs, 2H). | 33 |
| 249 | 390 | | CH | CH | N-(2-Amino-phenyl)-4-[(6-methoxy-pyridin-2-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.60 (bs, 1H), 7.96 (d, J=7.9 Hz, 1H), 7.52-7.50 (m, 2H), 7.37-7.30 (m, 1H), 7.25-7.21 (m, 2H), 7.19-6.99 (m, 1H), 6.84-6.81 (m, 1H), 6.67-6.64 (m, 1H), 6.11-6.07 (m, 1H), 5.93-5.89 (m, 1H), 4.93 (bs, 2H), 4.56 (d, J=5.8 Hz, 2H), 3.80 (s, 3H). | 37 |
| 250 | 391 | | CH | CH | N-(2-Amino-phenyl)-4-(quinolin-8-ylsulfanylmethyl)-benzamide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.68 (bs, 1H), 8.95 (bs, 2H), 8.43-8.38 (m, 1H), 7.90 (bs, 2H), 7.80-7.55 (m, 6H), 7.22 (d, J=7.7 Hz, 1H), 7.03 (d, J=7.7 Hz, 1H), 6.63 (d, J=7.4 Hz, 1H), 5.05 (bs, 2H), 4.48 (d, J=7.7, 2H). | 11 |

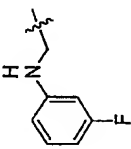
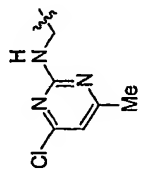
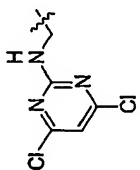
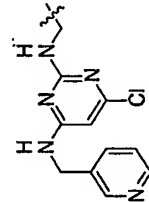
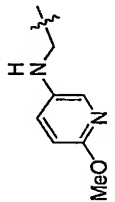
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|--|----|----|---|---|------|
| 251 | 392 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(2,6-dimethoxy-pyrimidin-4-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.84 (t, J=5.9 Hz, 1H), 7.46 (d, J=7.46 Hz, 2H), 7.20 (d, J=7.9 Hz, 1H), 7.04 (d, J=6.6 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.64 (dd, J=7.7, 7.4 Hz, 1H), 5.51 (bs, 1H), 4.57 (bs, 2H), 3.82 (s, 3H), 3.84 (s, 3H). | 37 |
| 252 | 393 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(3,5-dimethoxy-benzylamino)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.63 (bs, 1H), 7.79 (d, J=8.5 Hz, 2H), 7.19 (d, J=6.6 Hz, 1H), 7.00 (dd, J=7.9, 7.1 Hz, 1H), 6.62 (t, J=6.0 Hz, 1H), 6.82 (dd, J=1.4, 7.9 Hz, 1H), 6.67 (d, J=8.8 Hz, 2H), 6.58 (bs, 2H), 6.42 (bs, 1H), 4.87 (bs, 2H), 4.34 (d, J=6.0 Hz, 2H), 3.77 (s, 6H). | 37 |
| 253 | 394 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(3-methoxy-phenylsulfanylmethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.29-7.20 (m, 2H), 7.02-6.95 (m, 2H), 6.84-6.79 (m, 1H), 6.67-6.62 (m, 1H), 6.57-6.54 (m, 1H), 6.44-6.41 (m, 1H), 4.93 (bs, 2H), 4.41 (bs, 2H), 3.79 (s, 3H). | 11 |
| 254 | 395 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(3,5-dimethoxy-phenoxy-methyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.72 (bs, 1H), 8.05 (d, J=8.2 Hz, 2H), 7.61 (d, J=7.9 Hz, 2H), 7.24 (d, J=7.4 Hz, 1H), 7.04 (dd, J=6.9, 7.1 Hz, 1H), 6.85 (d, J=6.9 Hz, 1H), 6.66 (dd, J=7.4, 7.7 Hz, 1H), 6.27 (s, 2H), 6.26 (s, 1H), 5.23 (s, 2H), 5.21 (bs, 2H), 3.77 (s, 6H). | 11 |
| 255 | 396 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(quinolin-2-yloxy-methyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.70 (bs, 1H), 8.35 (d, J=9.1 Hz, 2H), 8.05 (d, J=7.9 Hz, 2H), 7.96 (d, J=7.9 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.76-7.69 (m, 2H), 7.51 (dd, J=6.9, 7.1 Hz, 1H), 7.24-7.16 (m, 2H), 7.02 (dd, J=6.9, 7.4 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 6.66 (d, J=7.4 Hz, 1H), 5.66 (s, 2H), 4.94 (bs, 2H). | 11 |

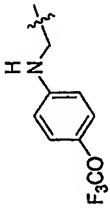
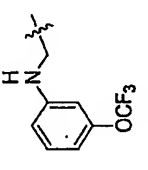
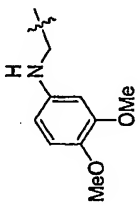
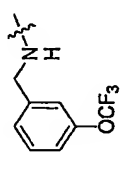
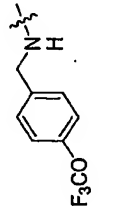
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 256 | 397 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(3,5-dimethoxy-phenylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.62 (bs, 1H), 7.96 (d, J=7.9 Hz, 2H), 7.49 (d, J=7.9 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 7.00 (dd, J=7.5, 7.9 Hz, 1H), 6.81 (d, J=7.9 Hz, 1H), 6.63 (dd, J=7.0, 8.0 Hz, 1H), 5.78 (s, 2H), 5.76 (s, 1H), 4.92 (bs, 2H), 4.35 (d, J=5.7, 2H), 3.65 (s, 6H). | 33 |
| 257 | 398 |  | CH | N | bis(<i>N</i> -(2-Amino-phenyl)-nicotinamide)-6-disulfide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.82 (bs, 2H), 9.08 (bs, 2H), 8.34 (d, J=8.3 Hz, 2H), 7.83 (d, J=8.3 Hz, 2H), 7.18 (d, J=7.5 Hz, 2H), 7.01 (dd, J=6.3, 7.0 Hz, 2H), 6.80 (d, J=7.9 Hz, 2H), 6.61 (t, J=7.03 Hz, 2H), 5.05 (bs, 4H). | 1 |
| 258 | 399 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-(isoquinolin-1-ylaminomethyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.90 (bs, 1H), 8.16 (bs, 2H), 7.65 (d, J=4.8 Hz, 2H), 7.54 (bs, 2H), 7.25 (d, J=7.0 Hz, 2H), 7.11 (bs, 2H), 7.07-7.02 (m, 2H), 6.84 (d, J=7.9 Hz, 1H), 6.67 (bs, 1H), 5.01 (bs, 2H), 4.88 (bs, 2H). | 33 |
| 259 | 400 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(2,3-dihydrobenzo[1,4]dioxin-6-ylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 7.97 (d, J=7.0 Hz, 2H), 7.51 (d, J=7.0 Hz, 2H), 7.22 (d, J=7.5 Hz, 1H), 7.02-6.97 (m, 1H), 6.84 (bs, 1H), 6.82-6.71 (m, 2H), 6.16 (d, J=6.6 Hz, 1H), 6.08 (s, 1H), 4.32 (bs, 2H), 4.16-4.13 (m, 4H). | 33 |
| 260 | 401 |  | CH | CH | 4-[(4-Acetylamino-phenylamino)-methyl]- <i>N</i> -(2-amino-phenyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.66 (bs, 1H), 9.56 (bs, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.53 (d, J=7.9 Hz, 2H), 7.28 (d, J=8.8 Hz, 2H), 7.22 (d, J=7.9 Hz, 1H), 7.02 (t, J=7.5 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.65 (t, J=7.5 Hz, 1H), 6.55 (d, J=8.3 Hz, 2H), 4.98 (bs, 2H), 4.38 (bs, 2H), 2.00 (s, 3H). | 33 |

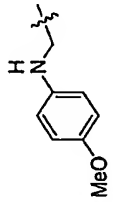
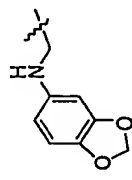
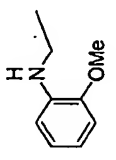
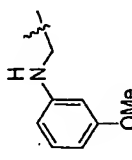
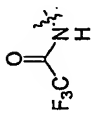
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 261 | 402 |  | CH | CH | <i>N</i> -(2-Amino-4-[(4-morpholin-4-yl)phenylamino]-methyl)-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.65 (bs, 1H), 7.98 (d, J=7.9 Hz, 2H), 7.52 (d, J=7.9 Hz, 2H), 7.21 (d, J=7.5 Hz, 1H), 7.02 (dd, J=7.0, 7.9 Hz, 1H), 6.83 (d, J=7.9 Hz, 1H), 6.78 (d, J=8.8 Hz, 2H), 6.64 (t, J=7.5 Hz, 1H), 6.55 (d, J=8.8 Hz, 2H), 4.94 (bs, 2H), 4.35 (d, J=5.7 Hz, 2H), 3.74 (t, J=4.4 Hz, 4H), 2.92 (t, J=4.4 Hz, 4H). | 33 |
| 262 | 403 |  | CH | CH | <i>N</i> -(2-Amino-4-[(4-methoxy-2-methylphenylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.64 (bs, 1H), 7.96 (d, J=7.6 Hz, 2H), 7.52 (d, J=7.6 Hz, 2H), 7.21 (d, J=8.2 Hz, 1H), 7.02 (t, J=8.2, 7.0 Hz, 1H), 6.83 (d, J=8.2 Hz, 1H), 6.71-6.53 (m, 3H), 6.32-6.30 (m, 1H), 4.94 (bs, 2H), 4.45 (d, J=5.9 Hz, 2H), 3.65 (s, 3H), 2.23 (s, 3H). | 33 |
| 263 | 404 |  | CH | CH | <i>N</i> -(2-Amino-4-[(2-cyano-4-methoxyphenylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.65 (bs, 1H), 7.98 (d, J=7.4 Hz, 2H), 7.56 (d, J=7.5 Hz, 2H), 7.19 (d, J=7.9 Hz, 1H), 6.99 (d, J=7.5 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.63 (t, J=6.6 Hz, 2H), 6.27 (s, 1H), 4.93 (bs, 2H), 4.55 (d, J=5.3 Hz, 2H), 3.69 (s, 6H). | 33 |
| 264 | 405 |  | CH | CH | <i>N</i> -(2-Amino-4-[(4-methoxy-3-(pyridin-3-ylmethoxy)-phenylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.62 (s, 1H), 8.72 (s, 1H), 8.49 (d, J=10.1 Hz, 1H), 7.93 (d, J=7.9 Hz, 2H), 7.68 (d, J=6.6 Hz, 1H), 7.37 (d, J=7.5 Hz, 2H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 6.78 (d, J=7.9 Hz, 1H), 6.69 (d, J=8.8 Hz, 1H), 6.62 (d, J=7.5 Hz, 1H), 6.23 (d, J=2.6 Hz, 1H), 6.09 (J=8.8 Hz, 1H), 5.76 (s, 1H), 4.64 (bs, 4H), 3.62 (s, 3H). | 33 |
| 265 | 406 |  | CH | CH | 2-[4-(2-Amino-phenylcarbamoyl)-benzylamino]-4,5-dimethoxy-benzoic acid | ¹ H-NMR (DMSO- <i>d</i> 6), δ (ppm): 9.67 (bs, 1H), 8.00 (d, J=7.9 Hz, 2H), 7.54 (d, J=7.9 Hz, 2H), 7.34 (s, 1H), 7.20 (d, J=7.9 Hz, 2H), 7.0 (t, J=7.9 Hz, 1H), 6.82 (d, J=7.9 Hz, 1H), 6.62 (t, J=7.9 Hz, 1H), 6.31 (s, 1H), 4.95 (bs, 2H), 4.62 (bs, 2H), 3.75 (s, 3H), 3.70 (s, 3H). | 33 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|--------|
| 266 | 407 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(3,5-dimethylphenylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> ₆), δ (ppm): 9.60 (s, 1H), 7.93 (d, J=7.9 Hz, 2H), 7.45 (d, J=7.9 Hz, 2H), 7.16 (d, J=7.5 Hz, 1H), 6.97 (t, J=7.5 Hz, 1H), 6.78 (d, J=7.9 Hz, 1H), 6.58 (t, J=7.0 Hz, 1H), 6.19-6.17 (m, 3H), 4.88 (s, 2H), 4.32 (d, J=5.7 Hz, 2H), 2.10 (s, 6H). | 33 |
| 267 | 408 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[[4-(pyridin-3-ylmethoxy)-phenylamino]-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> ₆), δ (ppm): 9.65 (s, 1H), 8.72 (s, 1H), 8.54 (s, 1H), 8.49 (d, J=10.9 Hz, 1H), 7.97 (d, J=7.9 Hz, 2H), 7.71 (d, J=7.9 Hz, 1H), 7.44 (d, J=8.3 Hz, 2H), 7.41-7.36 (m, 1H), 7.20 (d, J=7.9 Hz, 1H), 7.00 (t, J=7.4 Hz, 1H), 6.83 (d, J=7.0 Hz, 1H), 6.70-6.60 (m, 4H), 4.62 (s, 4H). | 33 |
| 268 | 409 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(2,4-dimethylphenylamino)-methyl]-benzamide | ¹ H-NMR (DMSO- <i>d</i> ₆), δ (ppm): 9.58 (s, 1H), 7.90 (d, J=7.9 Hz, 2H), 7.45 (d, J=7.5 Hz, 2H), 7.15 (d, J=7.5 Hz, 1H), 6.96 (t, J=7.5 Hz, 1H), 6.79 (s, 1H), 6.76 (d, J=9.6 Hz, 1H), 6.68 (d, J=7.9 Hz, 1H), 6.59 (t, J=7.0 Hz, 1H), 6.22 (d, J=7.9 Hz, 1H), 4.89 (bs, 2H), 4.39 (d, J=5.7 Hz, 2H), 2.15 (s, 3H), 2.10 (s, 3H). | 33 |
| 269 | 410 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(2,4,6-trimethylphenylamino)-methyl]-benzamide | ¹ H-NMR (CD ₃ OD), δ (ppm): 7.91 (d, J=7.9 Hz, 2H), 7.43 (d, J=8.5 Hz, 2H), 7.18 (d, J=7.5 Hz, 1H), 7.08 (t, J=7.5 Hz, 1H), 6.92 (d, J=7.9 Hz, 1H), 6.77 (s, 3H), 4.15 (bs, 2H), 2.19 (s, 9H). | 33 |
| 270 | 411 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(4-chloro-6-morpholin-4-ylpyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO- <i>d</i> ₆) δ *** (ππ): 9.66 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.82 (m, 1H), 7.47 (d, J = 7.7 Hz, 2H), 7.21 (d, J = 8.2 Hz, 1H), 7.03 (dd, J = 7.1, 7.1 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.65 (dd, J = 7.4, 7.4 Hz, 1H), 6.17 (bs, 1H), 4.94 (s, 2H, NH ₂), 4.53 (d, J = 5.8 Hz, 2H), 3.58 (m, 4H), 3.62 (m, 4H). | 24, 33 |

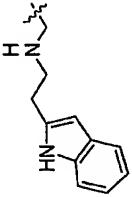
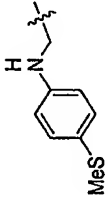
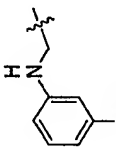
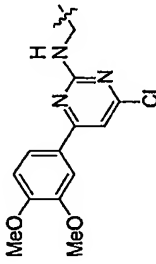
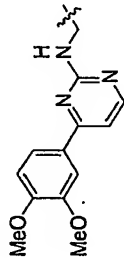
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 271 | 412 |  | CH | CH | N-(2-Amino-phenyl)-4-(3,4,5-trimethoxybenzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.33 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.99 (m, 1H), 6.87 (dd, J = 6.0, 5.8 Hz, 1H), 6.82 (m, 1H), 6.77 (s, 2H), 6.71 (d, J = 8.8 Hz, 2H), 6.64 (m, 1H), 4.87 (s, 2H, NH ₂), 4.32 (d, J = 5.5 Hz, 2H), 3.81 (s, 6H, 3, 4, 5-OMe), 3.79 (s, 3H, OMe). | 33 |
| 272 | 413 |  | CH | CH | N-(2-Amino-phenyl)-4-(4-fluorobenzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.45 (dd, J = 5.8, 8.5 Hz, 2H), 7.21 (m, 3H), 6.91 (m, 2H), 6.81 (dd, J = 1.1, 8.0 Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.62 (dd, J = 1.0, 7.2 Hz, 1H), 4.86 (s, 2H, NH ₂), 4.39 (d, J = 6.0 Hz, 2H). | 33 |
| 273 | 414 |  | CH | CH | N-(2-Amino-phenyl)-4-(4-methoxybenzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.31 (s, 1H), 7.79 (dd, J = 1.1, 8.5 Hz, 2H), 7.33 (d, J = 7.1 Hz, 2H), 7.19 (d, J = 7.7 Hz, 1H), 6.97 (m, 3H), 6.84 (m, 2H), 6.65 (m, 3H), 4.86 (s, 2H, NH ₂), 4.33 (d, J = 5.5 Hz, 2H), 3.58 (d, J = 1.6 Hz, 3H). | 33 |
| 274 | 415 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-fluorophenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 1H), 7.02 (ddd, J = 1.6, 7.1, 8.2 Hz, 1H), 6.93 (dd, J = 8.8, 9 Hz, 2H), 6.83 (dd, J = 1.1, 8.0 Hz, 1H), 6.63 (m, 3H), 6.35 (t, J = 6.2 Hz, 1H), 4.94 (s, 2H, NH ₂), 4.38 (d, J = 6.3 Hz, 2H). | 33 |
| 275 | 416 |  | CH | CH | N-(2-Amino-phenyl)-4-(3-fluorobenzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.32 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.44 (m, 1H), 7.26 (m, 1H), 7.18 (dd, J = 1.4, 8.0 Hz, 2H), 7.12 (ddd, J = 1.7, 8.0, 8.2 Hz, 1H), 6.99 (m, 2H), 6.81 (dd, J = 1.4, 8.0 Hz, 1H), 6.67 (dd, J = 1.6, 8.8 Hz, 2H), 6.62 (dd, J = 1.4, 7.4 Hz, 1H), 4.87 (s, 2H, NH ₂), 4.45 (d, J = 6.0 Hz, 2H). | 33 |

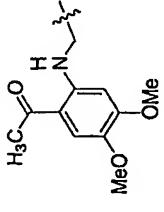
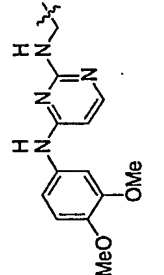
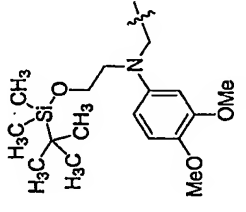
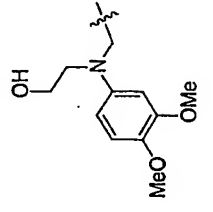
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|--------|
| 276 | 417 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3-fluorophenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 6.99-7.14 (m, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.76 (m, 1H), 6.64 (dd, J = 7.4, 7.4 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 6.34 (m, 2H), 4.94 (s, 2H, NH ₂), 4.41 (d, J = 6.0 Hz, 2H). | 33 |
| 277 | 418 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-methyl-pyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9.66 (s, 1H), 8.23 (m, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 (ddd, J = 1.5, 7.1, 8.0 Hz, 1H), 6.83 (dd, J = 1.5, 8.1 Hz, 1H), 6.65 (m, 2H), 4.94 (s, 2H, NH ₂), 4.61 (m, 2H), 2.32 (s, 3H). | 33 |
| 278 | 419 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4,6-dichloro-pyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9.69 (s, 1H), 8.82 (m, 1H), 7.99 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.7 Hz, 1H), 7.0 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.67 (m, 1H), 5.0 (bs, 2H, NH ₂), 4.60 (d, J = 6.3 Hz, 2H). | 33 |
| 279 | 420 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-[(pyridin-3-ylmethyl)-amino]-pyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9.87 (s, 1H), 8.49 (bs, 2H), 7.26-8.02 (bm, 8H), 7.22 (d, J = 8.0 Hz, 1H), 7.03 (dd, J = 7.4, 7.4 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.1, 8.0 Hz, 1H), 5.86 (bs, 1H), 4.95 (s, 2H, NH ₂), 4.51 (m, 2H). | 24, 33 |
| 280 | 421 |  | CH | CH | N-(2-Amino-phenyl)-4-[(6-methoxy-pyridin-3-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-D ₆) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 7.5 Hz, 7.9 Hz, 1H), 7.12 (dd, J = 3.08 Hz, 8.79 Hz, 1H), 7.02 (dd, J = 7.0 Hz, 7.5 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (m, 2H), 6.15 (t, J = 6.16 Hz, 1H), 4.94 (s, 2H, NH ₂), 4.39 (d, J = 6.15 Hz, 2H), 3.75 (s, 3H). | 33 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|------|------|---|----|----|--|--|------|
| 281 | 422 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-trifluoromethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 9.1 Hz, 2H), 7.03 (dd, J = 7.1, 8.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.71 (t, J = 6.0 Hz, 1H), 6.63-6.67 (m, 3H), 4.94 (s, 2H, NH ₂), 4.42 (d, J = 6.0 Hz, 2H). | 33 |
| 282 | 423 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3-trifluoromethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.67 (s, 1H), 8.00 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.19 (m, 2H), 7.03 (ddd, J = 1.5, 8.0, 8.8 Hz, 1H), 6.85 (m, 2H), 6.63 (m, 2H), 6.55 (s, 1H), 6.50 (m, 1H), 4.94 (s, 2H, NH ₂), 4.44 (d, J = 6.0 Hz, 2H). | 33 |
| 283a | 424b |  | CH | CH | N-(2-Amino-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.9 Hz, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.49 Hz, 7.49 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NH ₂), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H). | 33 |
| 284 | 425 |  | CH | CH | N-(2-Amino-phenyl)-4-(3-trifluoromethoxy-benzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.31 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.45-7.56 (m, 2H), 7.39 (s, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.18 (d, J = 6.6 Hz, 1H), 6.96-7.03 (m, 2H), 6.81 (d, J = 6.9 Hz, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 7.7 Hz, 1H), 4.86 (s, 2H, NH ₂), 4.48 (d, J = 5.8 Hz, 2H). | 33 |
| 285 | 426 |  | CH | CH | N-(2-Amino-phenyl)-4-(4-trifluoromethoxy-benzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 1.4, 7.7 Hz, 1H), 6.99 (ddd, J = 1.4, 8.0, 8.5 Hz, 2H), 6.81 (dd, J = 1.4, 8.0, 1H), 6.68 (d, J = 8.8 Hz, 2H), 4.85 (s, 2H, NH ₂), 4.45 (d, J = 6.0 Hz, 2H). | 33 |

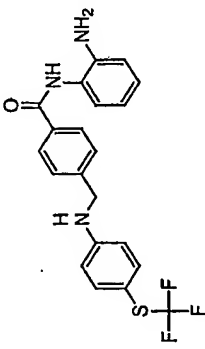
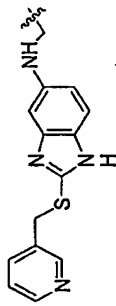
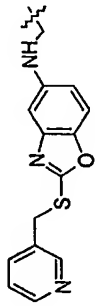
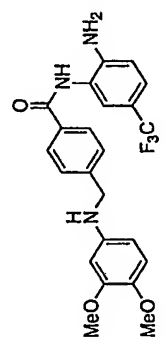
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 286 | 427 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-methoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.64 (s, 1H), 7.97 (d, J = 8.2 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 1.4, 8.0 Hz, 1H), 7.02 (ddd, J = 1.4, 7.4, 8.0 Hz, 1H), 6.83 (dd, J = 1.4, 8.0 Hz, 1H), 6.74 (m, 2H), 6.65 (ddd, J = 1.4, 7.7, 8.8 Hz, 1H), 6.58 (m, 2H), 5.99 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH ₂), 4.36 (d, J = 6.0 Hz, 2H), 3.68 (s, 3H). | 33 |
| 287 | 428 |  | CH | CH | N-(2-Amino-phenyl)-4-(benzo[1,3]dioxol-5-ylaminomethyl)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.0, 7.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.63-6.69 (m, 2H), 6.33 (d, J = 2.2 Hz, 1H), 6.15 (t, J = 6.16 Hz, 1H), 6.04 (dd, J = 2.2, 8.4 Hz, 1H), 5.86 (s, 2H), 4.94 (s, 2H, NH ₂), 4.35 (d, J = 6.16 Hz, 2H). | 33 |
| 288 | 429 |  | CH | CH | N-(2-Amino-phenyl)-4-[(2-methoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.63 (s, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.7 Hz, 1H), 7.02 (ddd, J = 1.4, 7.1, 8.0 Hz, 1H), 6.86 (m, 2H), 6.56-6.75 (m, 3H), 6.43 (dd, J = 1.6, 7.7 Hz, 1H), 5.75 (t, J = 6.3 Hz, 1H), 4.93 (s, 2H, NH ₂), 4.47 (d, J = 6.3 Hz, 2H), 3.88 (s, 3H). | 33 |
| 289 | 430 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3-methoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.61 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.2 Hz, 2H), 7.21 (dd, J = 1.1, 7.7 Hz, 1H), 6.97-7.05 (m, 2H), 6.82 (dd, J = 1.2, 8.1 Hz, 1H), 6.46 (ddd, J = 1.4, 7.7, 8.0 Hz, 1H), 6.41 (t, J = 6.3 Hz, 1H), 6.16-6.25 (m, 3H), 4.93 (s, 2H, NH ₂), 4.39 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H). | 33 |
| 290 | 431 |  | CH | CH | N-(2-Amino-phenyl)-4-(2,2,2-trifluoroacetylaminomethyl)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 11.53 (s, 1H), 9.71 (s, 1H), 8.08 (d, J = 8.2 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 7.6 Hz, 1H), 7.03 (dd, J = 7.0, 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (dd, J = 7.0, 7.6 Hz, 1H), 4.96 (s, 2H, NH ₂). | 14 |

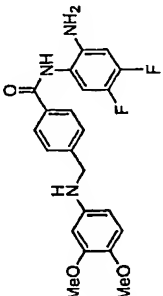
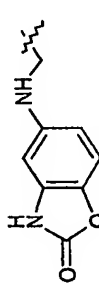
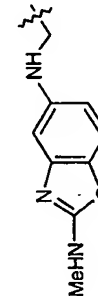
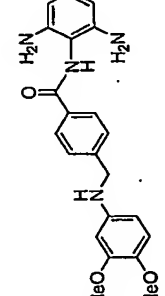
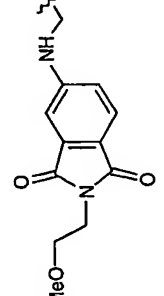
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|--|-----------|
| 291 | 432 | | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-(3,4,5-trimethoxybenzylamino)-pyrimidin-2-ylamino]-methyl}-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.64 (s, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.70 (bs, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.03 (dd, J = 7.0, 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.60-6.72 (m, 3H), 5.87 (s, 1H), 4.93 (s, 2H, NH ₂), 4.54 (d, J = 6.2 Hz, 2H), 4.43 (bs, 2H), 3.78 (s, 6H), 3.68 (s, 3H). | 24, 33 |
| 292 | 433 | | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-(3,4,5-trimethoxybenzylamino)-pyrimidin-2-ylamino]-methyl}-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.65 (s, 1H), 9.43 (s, 1H), 7.97 (m, 3H), 7.46 (bs, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (m, 3H), 6.83 (d, J = 7.0 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.08 (s, 1H), 4.93 (s, 2H, NH ₂), 4.69 (bs, 2H), 3.65 (s, 9H). | 24, 33 |
| 293 | 434 | | CH | CH | N-(2-Amino-phenyl)-4-(3,4-dimethoxybenzylamino)-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.31 (s, 1H), 7.79 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 7.04 (s, 1H), 6.92-7.01 (m, 3H), 6.80-6.87 (m, 2H), 6.69 (d, J = 8.8 Hz, 2H), 6.62 (m, 1H), 4.87 (s, 2H, NH ₂), 4.32 (d, J = 5.7 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H). | 33 |
| 294 | 435 | | CH | CH | N-(2-Amino-phenyl)-4-[(4-morpholin-4-ylpyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.64 (s, 1H), 7.95 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 7.9 Hz, 1H), 7.47 (d, J = 7.9 Hz, 2H), 7.31 (bs, 1H), 7.21 (d, J = 7.5, 1H), 7.02 (dd, J = 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.0, 7.0 Hz, 1H), 6.09 (d, J = 6.2 Hz, 1H), 4.94 (s, 2H, NH ₂), 4.54 (d, J = 5.7 Hz, 2H), 3.67 (s, 4H), 3.53 (s, 4H). | 24, 1, 33 |

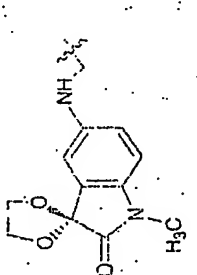
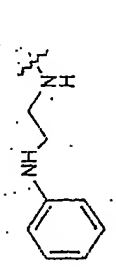
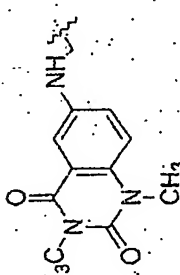
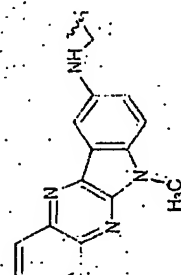
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|-----------|
| 295 | 436 |  | CH | CH | N-(2-Amino-phenyl)-4-{[2-(1H-indol-3-yl)-ethylamino]-methyl}-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.82 (s, 1H), 9.65 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 7.18-7.23 (m, 2H), 7.11 (dd, J = 7.0, 8.0 Hz, 1H), 7.01 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.51 (dd, J = 7.5, 6.6 Hz, 1H), 4.93 (s, 2H, NH ₂), 3.89 (s, 2H), 2.89 (m, 4H). | 57 |
| 296 | 437 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-methylsulfonylphenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.67 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.03 (dd, J = 7.5, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.53 (m, 4H), 4.95 (s, 2H, NH ₂), 4.41 (d, J = 5.7 Hz, 2H), 2.37 (s, 3H). | 33 |
| 297 | 438 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3-methylsulfonylphenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.03 (m, 2H), 6.83 (d, J = 7.9 Hz, 1H), 6.65 (dd, J = 7.5, 7.5 Hz, 1H), 6.39-6.51 (m, 4H), 4.94 (s, 2H, NH ₂), 4.41 (d, J = 5.7 Hz, 2H), 2.42 (s, 3H). | 33 |
| 298 | 439 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-chloro-6-(3,4-dimethoxyphenyl)pyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 8.37 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.68-7.79 (m, 2H), 7.55 (bs, 2H), 7.37 (s, 1H), 7.20 (d, J = 7.1 Hz, 1H), 7.11 (bs, 1H), 7.02 (dd, J = 7.5, 7.5 Hz, 1H), 6.82 (d, J = 7.9 Hz, 1H), 6.64 (dd, J = 7.5, 7.5 Hz, 1H), 4.93 (s, 2H, NH ₂), 4.86 (s, 2H), 3.88 (s, 6H). | 15, 33 |
| 299 | 440 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-(3,4-dimethoxyphenyl)pyrimidin-2-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.64 (s, 1H), 8.35 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.89 (m, 1H), 7.72 (m, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.2 (d, J = 5.3 Hz, 2H), 7.10 (d, J = 8.4 Hz, 1H), 7.01 (m, 1H), 6.82 (d, J = 7.0 Hz, 1H), 6.41 (t, J = 7.5 Hz, 1H), 4.92 (s, 2H, NH ₂), 4.68 (d, J = 6.2 Hz, 2H), 3.82 (s, 6H). | 15, 1, 33 |

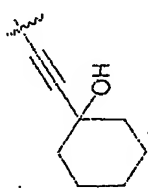
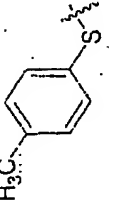
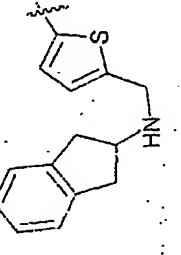
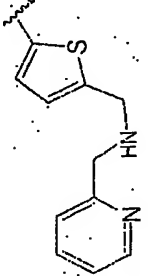
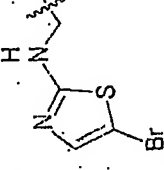
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|--|----|----|--|---|--------|
| 300 | 441 |  | CH | CH | 4-[(2-Amino-phenyl)-4-{[(3,4-dimethoxyphenyl)-2-methyl-N-(2-amino-phenyl)-benzamide] | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.68 (s, 1H), 9.45 (t, J = 5.7 Hz, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.32 (s, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 6.6, 7.5 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.31 (s, 1H), 4.95 (s, 2H, NH ₂), 4.63 (d, J = 5.7 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H). | 33 |
| 301 | 442 |  | CH | CH | N-(2-Amino-phenyl)-4-{[(3,4-dimethoxyphenyl)-2-pyrimidin-2-ylamino]-methyl}-benzamide | ¹ H NMR (300 MHz, CD ₃ OD+CDCl ₃) δ (ppm): 7.99 (d, J = 7.9 Hz, 2H), 7.80 (d, J = 6.2 Hz, 1H), 7.76 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.27 (m, 1H), 7.14 (m, 1H), 7.05 (dd, J = 2.2, 8.8 Hz, 1H), 6.95 (d, J = 7.9 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.08 (d, J = 6.2 Hz, 1H), 4.75 (s, 2H), 3.79 (s, 3H), 3.42 (s, 3H). | 1, 33 |
| 302 | 443 |  | CH | CH | N-(2-Amino-phenyl)-4-{[(2-(tert-butyl)-dimethyl-silanyloxy)-ethyl]- (3,4-dimethoxyphenyl)-amino]-methyl}-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.66 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 6.6, 8.4 Hz, 1H), 6.83 (d, J = 7.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.0 Hz, 1H), 6.44 (d, J = 2.6 Hz, 1H), 6.19 (dd, J = 2.6, 8.8 Hz, 1H), 4.93 (s, 2H), 4.67 (s, 2H), 3.88 (t, J = 5.7 Hz, 2H), 3.71 (s, 3H), 3.67 (s, 3H), 3.60 (t, J = 5.5 Hz), 0.96 (s, 9H), 0.06 (s, 6H). | 33 |
| 303 | 444 |  | CH | CH | N-(2-Amino-phenyl)-4-{[(3,4-dimethoxyphenyl)-(2-hydroxy-ethyl)-amino]-methyl}-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.65 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.21 (d, J = 7.5 Hz, 1H), 7.02 (dd, J = 7.0, 7.5 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 7.0, 7.5 Hz, 1H), 6.44 (s, 1H), 6.19 (d, J = 8.8 Hz, 1H), 4.94 (s, 2H), 4.79 (m, 1H), 4.66 (s, 2H), 3.67 and 3.71 (2s and broadening underneath, 8H), 3.55 (m, 2H). | 33, 23 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 304 | 445 | | CH | N | N-(2-Amino-phenyl)-6-[(3,4,5-trimethoxy-phenylamino)-methyl]-nicotinamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.82 (s, 1H), 9.13 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 7.03 (dd, J = 7.4, 7.7 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.40 (dd, J = 7.4, 7.7 Hz, 1H), 6.31 (t, J = 5.8 Hz, 1H), 5.96 (s, 2H), 5.01 (s, 2H), 4.48 (d, J = 5.8 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H). | 33 |
| 305 | 446 | | CH | N | N-(2-Amino-phenyl)-6-[2-(4-oxo-4H-quinazolin-3-yl)-ethylamino]-nicotinamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 8.69 (d, J = 2.2 Hz, 1H), 8.46 (s, 1H), 8.40 (d, J = 8.8 Hz, 1H), 8.32-8.36 (m, 1H), 7.91-7.96 (m, 1H), 7.77 (m, 1H), 7.67 (m, 1H), 7.5 (m, 4H), 7.2 (s, 1H), 4.46 (t, J = 5.9 Hz, 1H), 4.09 (t, J = 5.9 Hz, 2H). | 3 |
| 306 | 447 | | CH | CH | N-(2-Amino-phenyl)-4-[bis(3-trifluoromethoxybenzyl)-amino]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.37 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.54 (dd, J = 7.9, 7.9 Hz, 2H), 7.18-7.37 (m, 6H), 7.17 (d, J = 7.0 Hz, 1H), 6.99 (dd, J = 7.0, 7.9 Hz, 1H), 6.82 (m, 3H), 6.63 (dd, J = 7.5, 7.5 Hz, 1H), 4.94 (s, 4H), 4.86 (s, 2H). | 33 |
| 307 | 448 | | CH | CH | N-(2-Amino-phenyl)-4-[(2-dimethylamino-benzothiazol-5-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.58 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.9 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.59 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.44 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 5.7 Hz, 1H), 4.88 (bs, 2H), 4.37 (d, J = 5.7 Hz, 2H), 3.06 (s, 6H). | 33 |
| 308 | 449 | | CH | CH | N-(2-Amino-phenyl)-4-[(2-oxo-2,3-dihydro-1H-benzimidazol-5-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 10.2 (s, 1H), 10.1 (s, 1H), 9.62 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.34 (d, J = 8.4 Hz, 1H), 6.34 (t, J = 8.4 Hz, 1H), 4.89 (bs, 2H), 4.72 (s, 2H). | 33 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|--|------|
| 309 | 450 |  | CH | CH | N-(2-Amino-phenyl)-4-[(4-trifluoromethylsulfonyl-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.60 (s, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.9 Hz, 1H), 7.11 (d, J = 6.2 Hz, 1H), 6.97 (t, J = 7.0 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 2H), 6.60 (t, J = 7.9 Hz, 1H), 4.88 (bs, 2H), 4.72 (d, J = 6.2 Hz, 2H). | 33 |
| 310 | 451 |  | CH | CH | N-(2-Amino-phenyl)-4-[(2-pyridin-3-ylmethylsulfonyl)-1H-benzimidazol-5-ylamino]-methyl}-benzamide | ¹ H NMR (300 MHz, CD ₃ OD) δ (ppm): 8.67 (d, J = 1.8 Hz, 1H), 8.47 (dd, J = 1.3, 4.4 Hz, 1H), 8.08 (s, 1H), 8.03 (d, J = 7.9 Hz, 2H), 7.92 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.36-7.30 (m, 3H), 7.20-7.15 (m, 1H); 7.08 (dt, J = 1.3, 8.4 Hz, 1H), 6.94 (dd, J = 1.3, 7.9 Hz, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.74 (d, J = 2.2 Hz, 1H), 6.65 (d, J = 1.8 Hz, 1H), 4.55 (s, 2H); 4.20 (bs, 2H); 3.36 (s, 2H). | 33 |
| 311 | 452 |  | CH | CH | N-(2-Amino-phenyl)-4-[(2-pyridin-3-ylmethylsulfonyl)-benzoxazol-5-ylamino]-methyl}-benzamide | ¹ H NMR (300 MHz, CD ₃ OD) δ (ppm): 8.60 (s, 1H), 8.36 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.87 (m, 1H); 7.47 (d, J = 7.9 Hz, 2H), 7.30 (t, J = 6.6 Hz, 1H), 7.20-7.15 (m, 2H); 7.04 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.73 (t, J = 7.5 Hz, 1H), 6.66 (s, 1H); 6.61 (d, J = 8.8 Hz, 1H), 4.87 (s, 2H); 4.45 (s, 2H); 4.37 (s, 2H); 3.35 (s, 2H). | 33 |
| 312 | 453 |  | | | N-(2-Amino-5-trifluoromethyl-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.21 (s, 1H); 7.90 (d, J = 8.4 Hz, 2H); 7.54 (m, 1H); 7.50 (d, J = 8.4 Hz, 2H); 7.41-7.34 (m, 2H); 6.87 (d, J = 8.4 Hz, 1H); 7.77 (d, J = 8.4 Hz, 1H); 6.35 (d, J = 2.2 Hz, 1H); 6.20 (dd, J = 2.2, 8.8 Hz, 1H); 4.43 (s, 2H); 4.29 (s, 2H); 3.84 (s, 6H). | 33 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|------|
| 313 | 454 |  | | | N-(2-Amino-4,5-difluoro-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.21 (s, 1H); 7.84 (d, J = 7.9 Hz, 2H); 7.45 (d, J = 7.9 Hz, 2H); 7.20 (dd, J = 2.6, 8.4 Hz, 1H); 6.76 (d, J = 8.8 Hz, 1H); 6.57 (dd, J = 3.9, 7.9 Hz, 1H); 6.32 (d, J = 2.6 Hz, 1H); 6.16 (dd, J = 2.6, 8.4 Hz, 1H); 4.40 (s, 2H); 3.82 (s, 9H). | 33 |
| 314 | 455 |  | CH | CH | N-(2-Amino-phenyl)-4-[(2-oxo-2,3-dihydro-benzooxazol-5-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.60 (s, 1H); 7.93 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); 7.16 (d, J = 7.5 Hz, 1H); 6.97 (m, 2H); 6.78 (d, J = 7.5 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 6.35 (t, J = 5.7 Hz, 1H); 6.27 (m, 2H); 4.88 (bs, 2H); 4.34 (d, J = 6.2 Hz, 2H). | 33 |
| 315 | 456 |  | CH | CH | N-(2-Amino-phenyl)-4-[(2-methylamino-benzothiazol-5-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 7.92 (d, J = 7.9 Hz, 2H); 7.66 (d, J = 4.4 Hz, 1H); 7.49 (d, J = 7.9 Hz, 2H); 7.26 (d, J = 8.4 Hz, 1H); 7.15 (d, J = 7.9 Hz, 1H); 6.96 (d, J = 8.4 Hz, 1H); 6.59 (t, J = 7.9 Hz, 1H); 6.53 (s, 1H); 6.40 (dd, J = 1.3, 8.4 Hz, 1H); 6.28 (t, J = 5.7 Hz, 1H); 4.88 (bs, 2H); 4.36 (d, J = 5.7 Hz, 2H); 2.85 (d, J = 4.4 Hz, 3H). | 33 |
| 316 | 457 |  | | | N-(2,6-Diamino-phenyl)-4-[(3,4-dimethoxy-phenylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, CDCl ₃) δ (ppm): 8.09 (s, 1H); 7.88 (d, J = 7.5 Hz, 2H); 7.48 (d, J = 7.5 Hz, 2H); 6.97 (d, J = 7.9 Hz, 1H); 6.73 (d, J = 8.4 Hz, 2H); 6.64 (d, J = 7.9 Hz, 1H); 6.29 (s, 1H); 6.14 (d, J = 8.4 Hz, 1H); 4.39 (s, 2H); 3.81 (s, 3H); 3.80 (s, 3H); 3.70 (bs, 5H). | 33 |
| 317 | 458 |  | CH | CH | N-(2-Amino-phenyl)-4-[(2-(2-methoxy-ethyl)-1,3-dioxo-2,3-dihydro-1H-indol-5-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.61 (s, 1H); 7.95 (d, J = 7.9 Hz, 2H); 7.73 (t, J = 5.7 Hz, 1H); 7.52 (d, J = 8.4 Hz, 1H); 7.47 (d, J = 7.9 Hz, 2H); 7.15 (d, J = 7.9 Hz, 1H); 6.97 (d, J = 7.5 Hz, 1H); 6.92 (bs, 1H); 6.86 (d, J = 8.4 Hz, 1H); 6.77 (d, J = 7.9 Hz, 1H); 6.59 (t, J = 7.5 Hz, 1H); 4.89 (bs, 2H); 4.54 (d, J = 5.7 Hz, 2H); 3.65 (t, J = 5.3 Hz, 2H); 3.47 (t, J = 5.3 Hz, 2H); 3.20 (s, 3H). | 33 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 318 | 459 |  | CH | CH | N-(2-Amino-phenyl)-4-[(3-oxo-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.59 (s, 1H); 7.92 (d, J = 8.3 Hz, 2H); 7.46 (d, J = 8.3 Hz, 2H); 7.15 (d, J = 7.5 Hz, 1H); 6.96 (t, J = 7.0 Hz, 1H); 6.78-6.71 (m, 3H); 6.62-6.54 (m, 2H); 6.26 (t, J = 7.5 Hz, 1H); 4.87 (s, 2H); 4.36-4.32 (m, 4H); 4.23-4.19 (m, 2H); 2.98 (s, 3H). | 33 |
| 319 | 460 |  | CH | N | N-(2-Amino-phenyl)-6-(2-phenylamino-ethylamino)-nicotinamide | ¹ H NMR (300 MHz, CD ₃ OD) δ (ppm): 8.67 (d, J = 2.2 Hz, 1H); 7.97 (dd, J = 2.5, 8.9 Hz, 1H); 7.58 (m, 1H); 7.51 (m, 1H); 7.15 (dd, J = 1.1, 7.7 Hz, 1H); 7.08 (m, 2H); 6.89 (dd, J = 1.4, 8.0 Hz, 1H); 6.76 (dt, J = 4.4, 7.7 Hz, 1H); 6.67 (d, J = 7.7 Hz, 2H); 6.60 (m, 2H); 4.87 (bs, 2H); 3.60 (t, J = 6.3 Hz, 2H); 3.35 (t, J = 6.3 Hz, 2H). | 33 |
| 320 | 461 |  | CH | CH | N-(2-Amino-phenyl)-4-[(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-6-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.59 (s, 1H); 7.92 (d, J = 7.9 Hz, 2H); 7.47 (d, J = 7.9 Hz, 2H); 7.22 (d, J = 8.8 Hz, 1H); 7.16-7.09 (m, 3H); 6.96 (t, J = 7.5 Hz, 1H); 6.76 (d, J = 7.9 Hz, 1H); 6.65-6.56 (m, 2H); 4.87 (s, 2H); 4.42 (d, J = 5.3 Hz, 2H); 3.44 (s, 3H); 3.26 (s, 3H). | 33 |
| 321 | 462 |  | CH | CH | N-(2-Amino-phenyl)-4-[(6-methyl-6H-indolo[2,3-b]quinoxalin-9-ylamino)-methyl]-benzamide | ¹ H NMR (300 MHz, DMSO-d ₆) δ (ppm): 9.60 (s, 1H); 8.19 (d, J = 8.4 Hz, 1H); 8.05 (d, J = 8.4 Hz, 1H); 7.95 (d, J = 7.9 Hz, 2H); 7.76 (t, J = 7.0 Hz, 1H); 7.65 (t, J = 7.9 Hz, 1H); 7.57 (d, J = 7.9 Hz, 2H); 7.54 (d, J = 8.8 Hz, 1H); 7.41 (d, J = 1.3 Hz, 1H); 7.22 (dd, J = 1.8, 8.8 Hz, 1H); 7.14 (d, J = 7.9 Hz, 1H); 6.95 (t, J = 7.5 Hz, 1H); 6.76 (t, J = 7.9 Hz, 1H); 6.57 (t, J = 7.5 Hz, 1H); 6.51 (bs, 1H); 4.86 (bs, 2H); 4.54 (d, J = 4.8 Hz, 2H); 3.85 (s, 3H). | 33 |

| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|--|---|-------|
| 322 | 463 |  | N | CH | <i>N</i> -(2-Amino-phenyl)-6-(1-hydroxy-cyclohexylethynyl)-nicotinamide | LRMS calc: 335.40, found: 336.1 (MH) ⁺ | 14, 3 |
| 323 | 464 |  | N | CH | <i>N</i> -(2-Amino-phenyl)-6-p-tolylsulfanyl-nicotinamide | LRMS calc: 335.42, found: 336.1 (MH) ⁺ | 14, 3 |
| 324 | 465 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[5-(indan-2-ylaminomethyl)-thiophen-2-ylmethyl]-benzamide | LRMS calc: 453.6, found: 454.2 (MH) ⁺ | 21 |
| 325 | 466 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[5-(pyridin-2-ylaminomethyl)-thiophen-2-ylmethyl]-benzamide | LRMS calc: 414.52, found: 415 (MH) ⁺ | 21 |
| 326 | 467 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[5-bromo-thiazol-2-ylaminomethyl]-benzamide | LRMS calc: 403.3, found: 404 (MH) ⁺ | 21 |

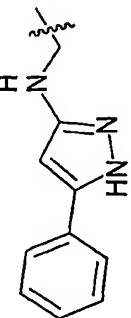
| Ex. | Cpd | W | Y | Z | Name | Characterization | Schm |
|-----|-----|---|----|----|---|---|------|
| 327 | 468 |  | CH | CH | <i>N</i> -(2-Amino-phenyl)-4-[(5-phenyl-1H-pyrazol-3-ylamino)-methyl]-benzamide | LRMS calc: 483.45, found: 484.1 (MH) ⁺ | 21 |

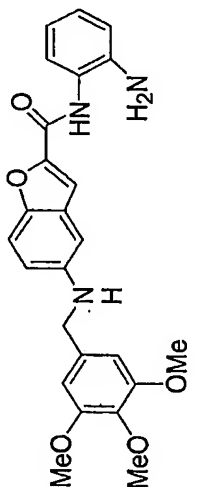
Table 4c

Characterization of Additional Compounds

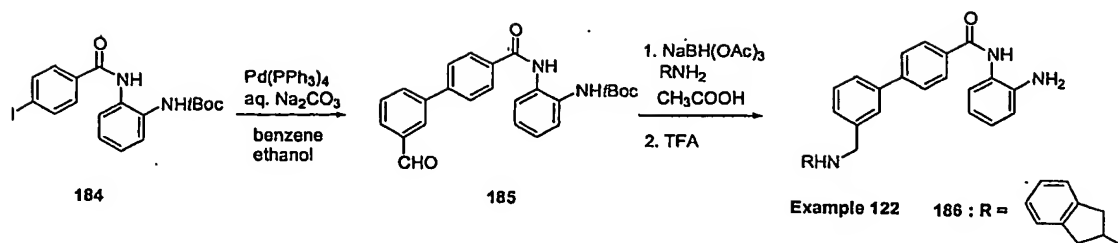
| Ex. | Cpd | Compound | Name | Characterization | Schm |
|-----|-----|----------|---|---|-----------|
| 426 | 571 | | N-(2-Hydroxyphenyl)-4-[(3,4,5-trimethoxyphenylamino)methyl]benzamide | $^1\text{H NMR}$ (DMSO- d_6): δ 9.57 (brs, 1H), 7.98 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.3 Hz, 2H), 7.07 (t, J = 8.3 Hz, 1H), 6.95 (d, J = 7.0 Hz, 1H), 6.85 (t, J = 7.9 Hz, 1H), 6.21 (t, J = 6.1 Hz, 1H), 5.95 (s, 2H), 4.38 (d, J = 5.7 Hz, 2H), 3.70 (s, 6H), 3.56 (s, 3H). | 33, 55 |
| 427 | 572 | | N-(2-hydroxyphenyl)-4-[(3,4-Dimethoxyphenylamino)methyl]benzamide | $^1\text{H NMR}$ (300 MHz, DMSO- d_6) δ (ppm): 9.9 (bs, 1H), 9.53 (s, 1H), 7.97 (d, J = 7.9 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.08 (dd, J = 7.5, 7.5 Hz, 1H), 6.96 (d, J = 7.9 Hz, 1H), 6.88 (dd, J = 7.5, 7.5 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.38 (s, 1H), 6.05 (m, 2H), 4.36 (d, J = 5.7 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H). | 33, 55 |
| 428 | 573 | | N-(4-Amino-3-thiophen-3-yl)-4-[[6-(2-morpholin-4-ylethoxy)benzothiazol-2-ylamino]methyl]benzamide | $^1\text{H NMR}$: (Acetone- d_6) δ (ppm): 9.09 (bs, 1H), 8.03 (d, J=7.9Hz, 2H), 7.96 (d, J=7.5 Hz, 1H), 7.65 (d, J=7.9 Hz, 2H), 7.61 (d, J=3.5 Hz, 1H), 7.51 (bs, 2H), 7.41 (d, J=8.8 Hz, 1H), 7.36 (s, 1H), 6.95 (d, J=6.2 Hz, 1H), 6.35 (d, J=3.5 Hz, 1H), 4.85 (s, 2H), 4.20 (t, J=5.7 Hz, 2H), 3.69 (t, J=4.4 Hz, 4H), 2.87-2.81 (m, 2H), 2.62-2.57 (m, 4H). | 33, 60 |

| Ex. | Cpd | Compound | Name | Characterization | Schm |
|-----|-----|----------|---|--|-----------|
| 429 | 574 | | N-(4-Amino-3-thiophen-3-yl)-4-[(3,4,5-trimethoxyphenylamino)methyl]benzamide | ¹ H NMR (DMSO-d ₆): δ 9.66 (brs, 1H), 7.94 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 7.9 Hz, 2H), 6.22-6.16 (m, 1H), 5.94 (s, 2H), 4.91 (s, 2H), 4.38 (d, J = 5.7 Hz, 4H), 3.70 (s, 6H), 3.55 (s, 3H). | 33, 60 |
| 430 | 575 | | N-(4-Amino-3-thiophen-3-yl)-4-(5-methoxy-1H-benzimidazol-2-ylsulfanylmethyl)benzamide | (DMSO) δ (ppm): 12.43 (bs, 1H), 9.59 (bs, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 3.7 Hz, 1H), 7.32 (bs, 1H, SCH), 6.96 (bs, 1H, SCH), 6.74 (dd, J = 8.8, 2.2 Hz, 1H), 6.11 (d, J = 3.7 Hz, 1H), 4.84 (s, 2H), 4.59 (s, 2H), 3.76 (s, 3 H). LRMS: 410.1 (calc) (M); 411.2 (found) (M+H)+ | 36, 60 |
| 431 | 576 | | 2-[4-(4-Methoxybenzylamino)phenyl]cyclopropanecarboxylic acid (2-amino-phenyl)amide | ¹ H-NMR (DMSO-d ₆), δ (ppm): 9.22 (bs, 1H), 8.19 (bs, 1H), 7.63 (d, J=7.1 Hz, 1H), 7.53 (t, J=4.2 Hz, 1H), 7.41 (dd, J=9.2, 1.5 Hz, 1H), 7.25 (d, J=8.3 Hz, 2H), 7.06 (d, J=7.1 Hz, 1H), 6.85 (d, J=8.3 Hz, 2H), 6.62-6.59 (m, 3H), 4.51 (d, J=4.2 Hz, 2H), 3.78 (s, 3H), 2.77 (d, J=3.1 Hz, 1H), 2.45 (d, J=1.1 Hz, 1H), 1.22 (m, 1H), 1.05 (m, 1H). | |
| 432 | 577 | | N-(2-Amino-4-(3-cyano-6-methylpyridin-2-yl)oxyphenyl)benzamide | ¹ H NMR (DMSO-d ₆) δ (ppm): 9.72 (brs, 1H), 8.23 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.9 Hz, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 6.65 (t, J = 7.5 Hz, 1H), 5.62 (brs, 2H), 4.97 (brs, 2H) | 11 |

| Ex. | Cpd | Compound | Name | Characterization | Schm |
|-----|-----|----------|---|--|--------|
| 433 | 578 | | N-(2-Amino-phenyl)-4-[(4-methoxy-6-methoxy-pyridin-3-yl)-pyrimidin-2-ylamino]-methylbenzamide | ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 9.63 (s, 1H), 8.95 (d, J = 2.2 Hz, 1H), 8.40 (d, J = 5.3 Hz, 2H), 7.96 (m, 3H), 7.54 (d, J = 7.5 Hz, 2H), 7.22 (dd, J = 5.3, 7.8 Hz, 2H), 7.01 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H), 6.64 (dd, J = 7.0, 7.9 Hz, 1H), 4.92 (s, 2H), 4.70 (d, J = 6.2 Hz, 2H), 3.98 (s, 3H). | 15, 33 |
| 434 | 579 | | 2-Acetylamino-5-[4-(2-amino-phenylcarbamoyl)-benzyl]-thiophene-3-carboxamide | ^1H NMR (DMSO) δ (ppm): 11.98 (bs, 1H), 9.61 (bs, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.81 (s, 1H), 7.45 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.19 (s, 1H), 7.16 (d, J = 7.3 Hz, 1H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 7.3, 7.3 Hz, 1H), 4.88 (bs, 2H), 4.10 (s, 2H), 2.15 (s, 3H). | 49 |
| 435 | 580 | | N-(2-Amino-phenyl)-4-[(3-methyl-2-methylamino-3H-benzimidazol-5-ylamino)-methyl]benzamide | ^1H NMR (DMSO) δ (ppm): 9.56 (s, 1H), 7.90 (d, J = 7.9 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.78 (dd, J = 13.2, 8.35 Hz, 2H), 6.58 (t, J = 7.5 Hz, 1H), 6.39 (s, 1H), 6.31 (m, 2H), 5.75 (t, J = 6.15 Hz, 1H), 4.87 (s, 2H), 4.32 (d, J = 5.7 Hz, 2H), 3.34 (s, 3H), 2.82 (d, J = 8.5 Hz, 3H). | 61 |
| 438 | 591 | | 5-(5-Methoxy-1H-benzimidazol-2-ylsulfanylmethyl)-benzofuran-2-carboxylic acid | ^1H NMR (DMSO) δ (ppm): 9.84 (s, 1H), 7.84 (s, 1H), 7.67 (s, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.78-6.74 (m, 3H), 6.59 (t, J = 7.5 Hz, 1H), 5.71 (s, 2H), 4.94 (s, 1H), 4.65 (s, 2H), 3.76 (s, 3H). | 64 |

| Ex. | Cpd | Compound | Name | Characterization | Schm |
|-----|-----|---|--|--|------|
| 439 | 592 |  | 5-(3,4,5-Trimethoxy-2-phenylamino)-2-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide | ¹ H NMR (DMSO) δ (ppm): 9.69 (s, 1H), 7.47 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.19 (d, J = 6.6 Hz, 1H), 6.97 (dd, J = 7.5, 7.5 Hz, 1H), 6.89 (dd, J = 8.8, 2.2 Hz, 1H), 6.79-6.78 (m, 2H), 6.74 (s, 2H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H), 6.14 (t, J = 5.7 Hz, 1H), 4.92 (s, 2H), 4.21 (d, J = 5.7 Hz, 1H), 3.75 (s, 6H), 3.31 (s, 3H). | 64 |

Scheme 21



Example 122

Step 1: {2-[(3'-Formyl-biphenyl-4-carbonyl)-amino]-phenyl}-carbamic acid tert-butyl ester (185)

[0254] Following the procedure described in Example 15, step 1, but, substituting 184 for 140, the title compound 185 was obtained in 74% yield. ¹H NMR (CDCl₃): δ 10.10 (s, 1H), 9.41 (s, 1H), 8.13 (m, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.89 (m, 2H), 7.77 (m, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.64 (m, 1H), 7.27-7.09 (m, 3H), 7.03 (s, 1H), 1.52 (s, 9H).

Step 2: N-(2-Aminophenyl)-4-[3-(indan-2-ylaminomethyl)phenyl]-benzamide (186)

[0255] To a stirred solution of biphenyl aldehyde (104 mg, 0.25 mmol) and 2-aminoindane (33.3 mg, 0.25 mmol) in dichloroethane (1mL) was added sodium triacetoxyborohydride (80 mg, 0.375 mmol) followed by a glacial acetic acid (15μl, 0.25 mmol), and then the mixture was stirred at room temperature for 3h. After a removal of the volatiles, the residue was partitioned between ethyl acetate and 10% aqueous sodium bicarbonate solution. The combined organic layers were washed with water, dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired Boc-monoprotected product (112mg, 84% yield) as a white solid. ¹H NMR (CDCl₃): δ 9.21 (s, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.83 (m, 1H), 7.69 (d, J = 8.7 Hz, 2H), 7.65 (s, 1H), 7.54-7.38 (m, 3H), 7.28 (m, 7H), 6.82 (s, 1H), 3.95 (s, 2H), 3.74 (m, 1H), 3.22 (dd, J = 15.6, 6.9 Hz, 2H), 2.89 (dd, J = 15.6, 6.6 Hz, 2H), 1.53 (s, 9H).

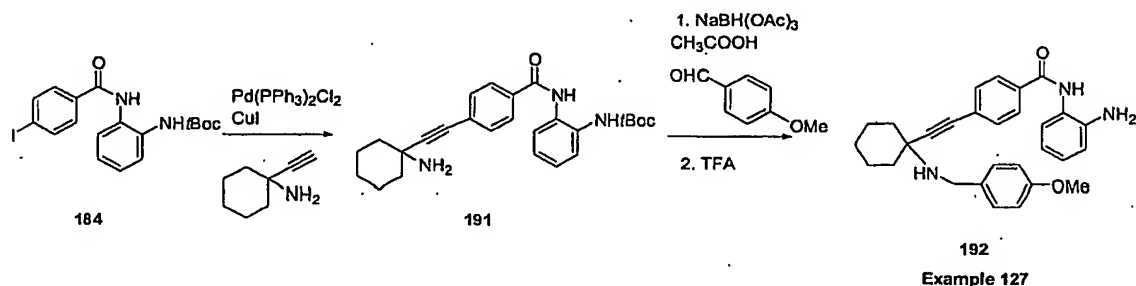
[0256] Following the procedure described in Example 42, step 3, but substituting the previous compound for 46, the title compound 186 was obtained in 98 % yield. ¹H NMR (20% CD₃OD in CDCl₃): δ 7.95 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.57 (m, 1H), 7.54-6.79 (m,

11H), 3.95 (s, 2H), 3.66 (m, 1H), 3.16 (dd, $J = 15.6, 6.9$ Hz, 2H), 2.81 (dd; $J = 15.6, 6.6$ Hz, 2H).

Examples 123-126

[0257] Examples 123 to 126 (compounds 187 - 190) were prepared using the same procedure as described for compound 186 in Example 122 (scheme 21).

Scheme 22



Example 127

Step 1: {2-[4-(1-Amino-cyclohexylethynyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (191)

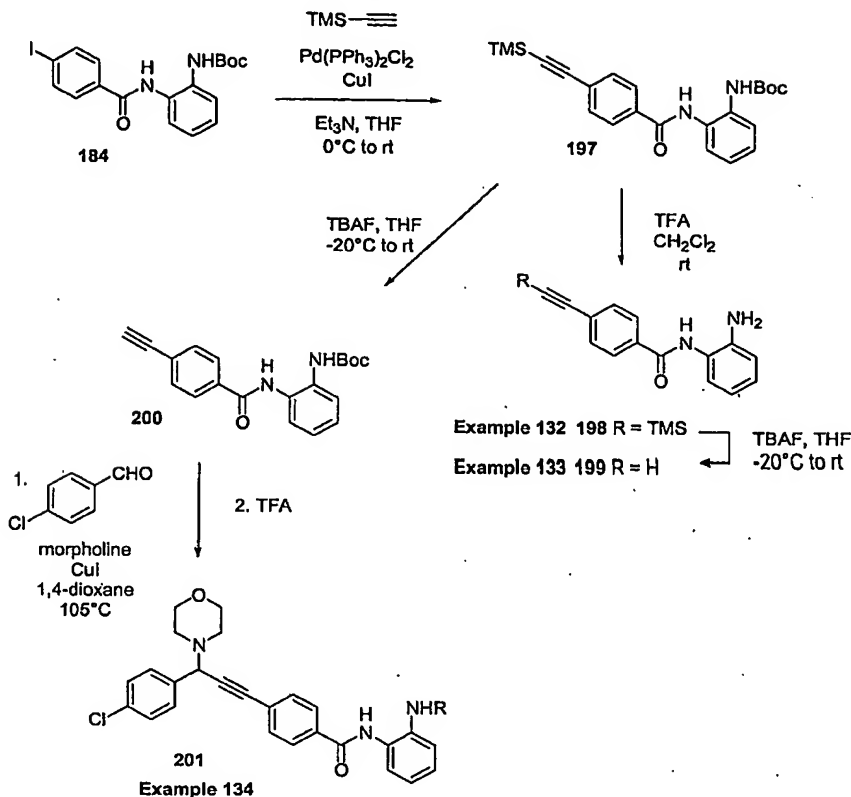
[0258] A mixture of iodide 184 (438 mg, 1.0 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (35 mg, 0.05 mmol), triphenylphosphine (7.6 mg, 0.025 mmol), and 1-ethynylcyclohexylamine (185 mg, 1.5 mmol) was stirred at room temperature in THF (4 mL) containing triethylamine (0.56 mL, 4.0 mmol) for 20 min. To this CuI (3.8 mg, 0.02 mmol) was added and stirring continued for 2 h. The reaction mixture was then diluted with ethyl acetate (30 mL), washed with water, and the organic layer was dried and concentrated. Purification by flash chromatography (10% methanol in chloroform) gave the desired product 191 (420 mg, 97% yield). ^1H NMR (CDCl_3): δ 9.36 (s, 1H), 7.94 (d, $J = 8.4$ Hz, 2H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.25-6.85 (m, 3H), 2.10-1.30 (m, 10H), 1.51 (s, 9H).

Step 2: N-(2-Aminophenyl)-4-[1-(4-methoxy-benzylamino)-cyclohexylethynyl]-benzamide (192)

[0259] Following the procedure described in Example 122, step 2, but substituting *p*-anisaldehyde for 2-aminoindane, the title compound 192 was obtained in 74 % yield. ^1H NMR (CDCl_3): δ 8.44 (s, 1H), 7.82 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.31 (d, J

= 8.4 Hz, 2H), 7.23 (m, 1H), 7.05 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.78 (m, 2H), 3.97 (s, 2H), 3.76 (s, 3H), 2.10-1.30 (m, 10H).

Scheme 23



Example 133

Step 1: N-[2-(t-Butyloxycarbonyl)-amino-phenyl]-4-(trimethylsilylethynyl)benzamide (197)

[0260] To a stirred solution of 184 (5.00 g, 11.41 mmol) in anhydrous THF (100 ml) under nitrogen at 0°C were added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (240 mg, 0.34 mmol), CuI (130 mg, 0.69 mmol), and trimethylsilylacetylene (2.10 ml, 14.84 mmol), respectively. Then, anhydrous Et_3N (6.36 ml, 45.66 mmol) was added dropwise. The temperature was slowly warmed up to room temperature over 4 h. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with ethyl acetate. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel

(AcOEt/hexane: 20/80→50/50) to afford the title compound **197** (4.42 g, 10.83 mmol, 94% yield) as a yellow powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.26 (bs, 1H), AB system (δ_A = 7.91, δ_B = 7.55, J = 8.3 Hz,

4H), 7.85 (d, $J = 7.9$ Hz, 1H), 7.32-7.13 (m, 3H), 6.70 (bs, 1H), 1.53 (s, 9H), 0.28 (s, 9H).

Step 2: N-(2-Amino-phenyl)-4-(trimethylsilylethynyl)benzamide (198)

[0261] Following the procedure described in Example 42, step 3, but substituting the previous compound for 46, the title compound 198 (70 mg, 0.23 mmol) was obtained as a white solid with a major fraction composed of a mixture of 198 and 199. ^1H NMR (300 MHz, acetone- d_6) δ (ppm): 9.20 (bs, 1H), AB system ($\delta_A = 8.07$, $\delta_B = 7.62$, $J = 8.2$ Hz, 4H), 7.32 (d, $J = 7.6$ Hz, 1H), 7.05 (td, $J = 7.6$, 1.2 Hz, 1H), 6.90 (d, $J = 7.6$ Hz, 1H), 6.72 (t, $J = 7.3$ Hz, 1H), 4.66 (bs, 2H), 0.30 (s, 9H).

Step 3: N-(2-Amino-phenyl)-4-ethynylbenzamide (199)

[0262] To a stirred solution at -20°C of a mixture of 198 and 199 in anhydrous THF (15 ml) under nitrogen was added a solution of TBAF (1 ml, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 18 h. Then, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl and diluted with ethyl acetate. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 30/70) to afford the title compound 199 (215 mg, 0.91 mmol, 46% yield over 2 steps) as a pale yellow powder. ^1H NMR (300 MHz, acetone- d_6) δ (ppm): 9.19 (bs, 1H), AB system ($\delta_A = 8.08$, $\delta_B = 7.66$, $J = 8.5$ Hz, 4H), 7.33 (d, $J = 7.6$ Hz, 1H), 7.05 (t, $J = 7.3$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 6.72 (t, $J = 7.6$ Hz, 1H), 4.67 (bs, 2H), 3.88 (s, 1H).

Example 134

Step 1: N-[2-(*t*-Butyloxycarbonyl)-amino-phenyl]-4-ethynylbenzamide (200)

[0263] To a stirred solution at -20°C of a mixture of 199 (3.48 g, 8.53 mmol) in anhydrous THF (50 ml) under nitrogen was slowly added a solution of TBAF (9.4 ml, 9.38 mmol, 1.0 M in THF). The reaction mixture was allowed to warm up to room temperature over 2 h and stirred at room temperature for 4 h. Then, the reaction mixture was concentrated, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was

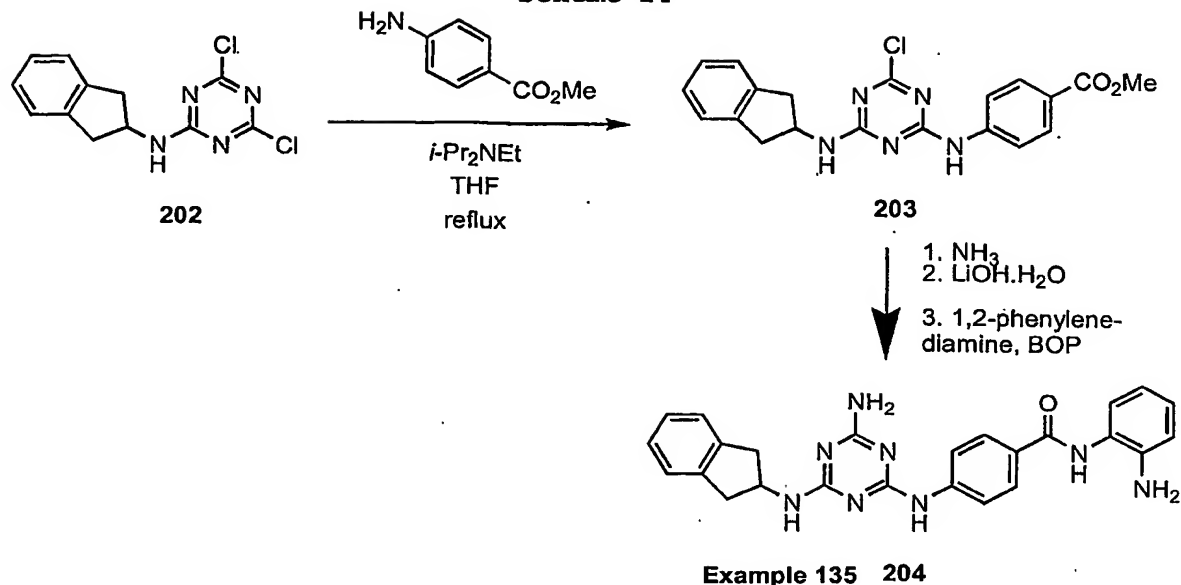
then purified by flash chromatography on silica gel (AcOEt/hexane: 25/75→30/70) to afford the title compound 200 (2.53 g, 7.53 mmol, 88% yield) as a pale yellow foam. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.31 (bs, 1H), AB system ($\delta_A = 7.94$, $\delta_B = 7.59$, $J = 8.5$ Hz, 4H), 7.83 (d, $J = 7.6$ Hz, 1H), 7.30-7.10 (m, 3H), 6.75 (bs, 1H), 3.23 (s, 1H), 1.53 (s, 9H).

Step 2: N-(2-amino-phenyl)-4-[3-(4-chlorophenyl)-3-morpholin-4-yl-1-propyn-1-yl]-benzamide (201)

To a stirred solution at room temperature of 200 (200 mg, 0.60 mmol) in anhydrous 1,4-dioxane (5 ml) under nitrogen were added 4-chlorobenzaldehyde (100 mg, 0.71 mmol), morpholine (60 μl , 0.68 mmol), and CuI (6 mg, 0.03 mmol), respectively. The reaction mixture was bubbled with nitrogen for 5 min and warmed up to 105°C. After 18 h, the reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate, and successively washed with a saturated aqueous solution of NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the desired compound (193 mg, 0.35 mmol, 59% yield) as a pale yellow foam. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.40 (bs, 1H), AB system ($\delta_A = 7.96$, $\delta_B = 7.36$, $J = 8.5$ Hz, 4H), 7.79 (d, $J = 7.9$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 4H), 7.25-7.10 (m, 3H), 6.91 (s, 1H), 4.80 (s, 1H), 3.82-3.68 (m, 4H), 2.69-2.58 (m, 4H), 1.53 (s, 9H).

[0264] Following the procedure described in Example 42, step 3, but substituting the previous compound for 46, the title compound 201 was obtained in 67 % yield. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ (ppm): 9.80 (bs, 1H), AB system ($\delta_A = 8.06$, $\delta_B = 7.71$, $J = 8.1$ Hz, 4H), AB system ($\delta_A = 7.65$, $\delta_B = 7.52$, $J = 8.3$ Hz, 4H), 7.20 (d, $J = 7.9$ Hz, 1H), 7.02 (t, $J = 7.3$ Hz, 1H), 6.82 (d, $J = 7.0$ Hz, 1H), 6.64 (t, $J = 7.5$ Hz, 1H), 5.10 (s, 1H), 4.97 (bs, 2H), 3.72-3.58 (m, 4H), 2.67-2.46 (m, 4H).

Scheme 24

**Example 135**

Step 1: Methyl 4-(4-chloro-6-(2-indanylamino)-[1,3,5]triazin-2-yl-amino)-benzoic ester (203)

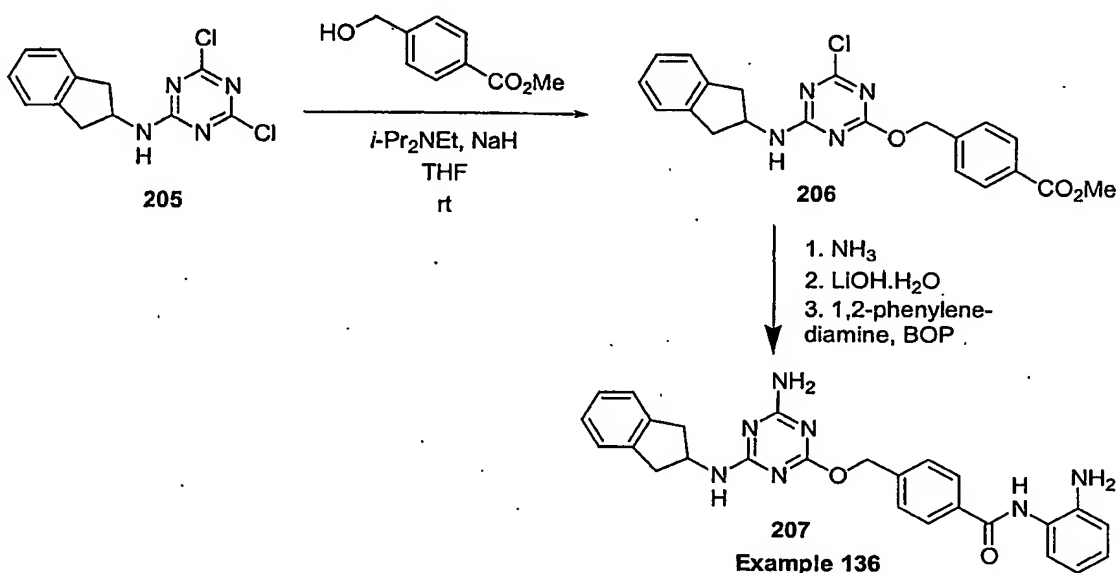
[0265] To a stirred solution at room temperature of 202 (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added *i*-Pr₂NEt (1.86 ml, 10.66 mmol) and methyl 4-aminobenzoate (1.29 g, 8.53 mmol) or ArNH₂ (1.2 equiv), respectively. The reaction mixture was then refluxed for 24 h. After cooling, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/CH₂Cl₂: 2/98→5/95) to afford the title compound 203 (1.70 g, 4.30 mmol, 60% yield) as a beige powder. ¹H NMR (300 MHz, CDCl₃) δ (ppm): mixture of rotamers, 2 AB system (δ_A = 8.03, δ_{A'} = 8.00, δ_B = 7.70, δ_{B'} = 7.61, J_{AB} = J_{A'B'} = 8.8 Hz, 4H), 7.43 and 7.31 (2 bs, 1H), 7.29-7.19 (m, 4H), 5.84 and 5.78 (2 d, J = 7.2 and 7.7 Hz, 1H), 4.98-4.77 (2 m, 1H), 3.91 and 3.90 (2 s, 3H), 3.41 (dd, J = 16.1, 7.0 Hz, 2H), 2.94 and 2.89 (2 dd, J = 15.9, 4.9 Hz, 2H).

Step 2: 4-[4-amino-6-(2-indanylamino)-[1,3,5]-triazin-2-ylamino]-N-(2-amino-phenyl)-benzamide (204)

[0266] The title compound 204 was obtained from 203 in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. ¹H

NMR (300 MHz, acetone- d_6) δ (ppm): mixture of rotamers, 8.98 (m, 1H), 8.49 and 8.28 (2m, 1H), 8.10-7.92 (m, 4H), 7.35-7.14 (m, 5H), 7.03 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 6.6, 1.3 Hz, 1H), 6.71 (td, J = 7.6, 1.3 Hz, 1H), 6.57 and 6.42 (2m, 1H), 6.04 and 5.86 (2m, 2H), 4.92-4.76 (m, 1H), 4.70-4.58 (m, 1H), 3.44-3.26 (m, 2H), 3.08-2.92 (m, 2H). HRMS (calc.): 452.2073, (found): 452.2062.

Scheme 25



Example 136

Step 1: Methyl 4-[(4-chloro-6-(2-indanyl-amino)-[1,3,5]triazin-2-yl)oxy]-methyl]-benzoic ester (206)

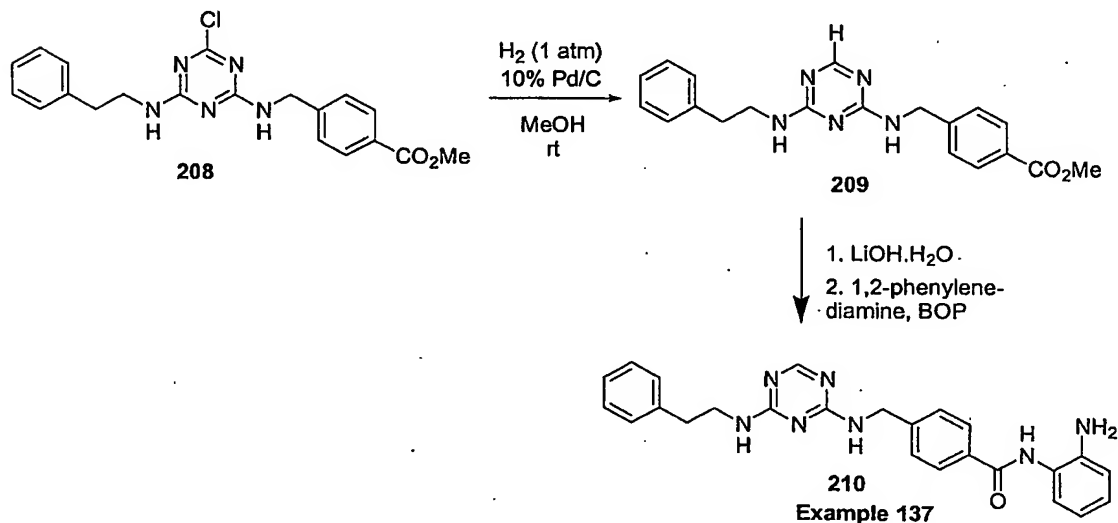
[0267] To a stirred solution at 0°C of 205 (2.00 g, 7.11 mmol) in anhydrous THF (50 ml) under nitrogen were added $i\text{-Pr}_2\text{NEt}$ (1.86 ml, 10.66 mmol) and methyl 4-(hydroxymethyl)benzoate (1.30 g, 7.82 mmol). After few minutes, NaH (95%, 186 mg, 7.11 mmol) was added portionwise. Then, the reaction mixture was allowed to warm to room temperature. After 24 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ CH_2Cl_2 : 2/98) to afford the title compound 206 (2.00 g, 4.88 mmol, 69% yield) as a colorless sticky foam. ^1H NMR (300 MHz, CDCl_3) δ (ppm): mixture of rotamers, 2 AB system (δ_A = 8.06, $\delta_{A'}$ = 8.03, δ_B = 7.52, $\delta_{B'}$ = 7.46, J_{AB} = $J_{A'B'}$ = 8.5.

Hz, 4H), 7.26-7.17 (m, 4H), 5.94 and 5.85 (2 bd, $J = 7.8$ Hz, 1H), 5.48 and 5.39 (2 s, 2H), 4.92-4.76 (2 m, 1H), 3.94 and 3.92 (2 s, 3H), 3.39 and 3.33 (2 dd, $J = 16.0, 7.0$ Hz, 2H), 2.89 and 2.84 (2 dd, $J = 16.0, 4.9$ Hz, 2H).

Step 2: 4-{[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yloxy]-methyl}-N-(2-amino-phenyl)-benzamide (207)

[0268] The title compound 207 was obtained from 206 in 3 steps following the same procedure as Example 1, Pathway B steps 3-5. ^1H NMR (300 MHz, acetone- d_6 + ϵ DMSO- d_6) δ (ppm): 9.49 (m, 1H), 8.12-8.03 (m, 2H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.35 (d, $J = 7.1$ Hz, 1H), 7.28-7.13 (m, 4H), 7.07-6.94 (m, 2H), 6.90 (dd, $J = 7.3, 1.4$ Hz, 1H), 6.70 (td, $J = 7.3, 1.1$ Hz, 1H), 6.44 (bs, 1H), 6.25 (bs, 1H), 5.47 and 5.41 (2s, 2H), 4.87-4.68 (m, 3H), 3.35-3.20 (m, 2H), 3.02-2.88 (m, 2H). HRMS (calc.): 467.2070, (found): 467.2063.

Scheme 26



Example 210

Methyl 4-[(4-chloro-6-phenethyl-amino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (208)

[0269] The title compound 208 was obtained from 2 following the same procedure as in Example 1, pathway B steps 2 ($\text{R}^1\text{R}^2\text{NH} =$ phenethylamine).

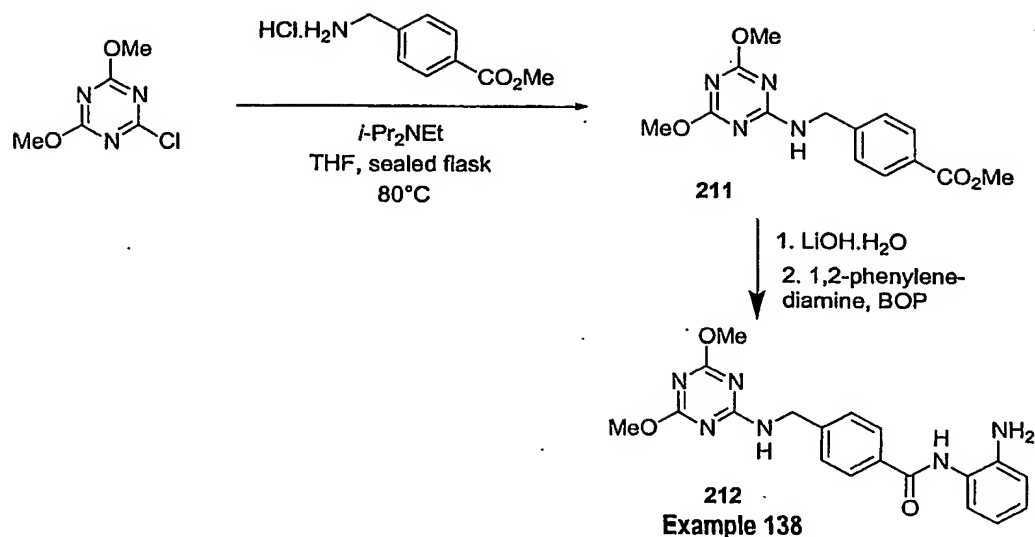
Step 1: Methyl 4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (209)

[0270] To a degazed solution of 208 (300 mg, 0.75 mmol) in MeOH (35 mL) was added 10% Pd/C (24 mg, 0.023 mmol). The reaction mixture was stirred under a 1 atm pressure of H₂ at room temperature for 20 h then it was purged with N₂. The palladium was removed by filtration through celite and the reaction mixture was concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/CH₂Cl₂: 4/96) to afford the title compound 209 (135 mg, 0.37 mmol, 50% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.08 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.50-7.15 (m, 6H), 4.85-4.65 (m, 2H), 3.98 (s, 3H), 3.82-3.62 (m, 2H), 3.05-2.85 (m, 2H).

Step 2: N-(2-Amino-phenyl)-4-[(4-phenethylamino-[1,3,5]triazin-2-yl-amino)-methyl]-benzamide (210)

[0271] The title compound 210 was obtained from 209 in 2 steps following the same procedure as in Example 1, steps 4 and 5. ¹H NMR: (300 MHz, acetone-d₆) δ (ppm): 9.03 (s, 1H), 8.17-7.87 (m, 3H), 7.49 (dd, J = 19.2, 8.2 Hz, 2H), 7.32-7.03 (m, 6H), 6.99 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.67 (t, J = 7.4 Hz, 1H), 6.60-6.30 (m, 2H), 4.72 (t, J = 6.3 Hz, 1H), 4.65-4.56 (m, 1H), 3.67-3.51 (m, 2H), 2.95-2.80 (m, 2H).

Scheme 27



Example 138

Step 1: Methyl 4-[(4,6-dimethoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (211)

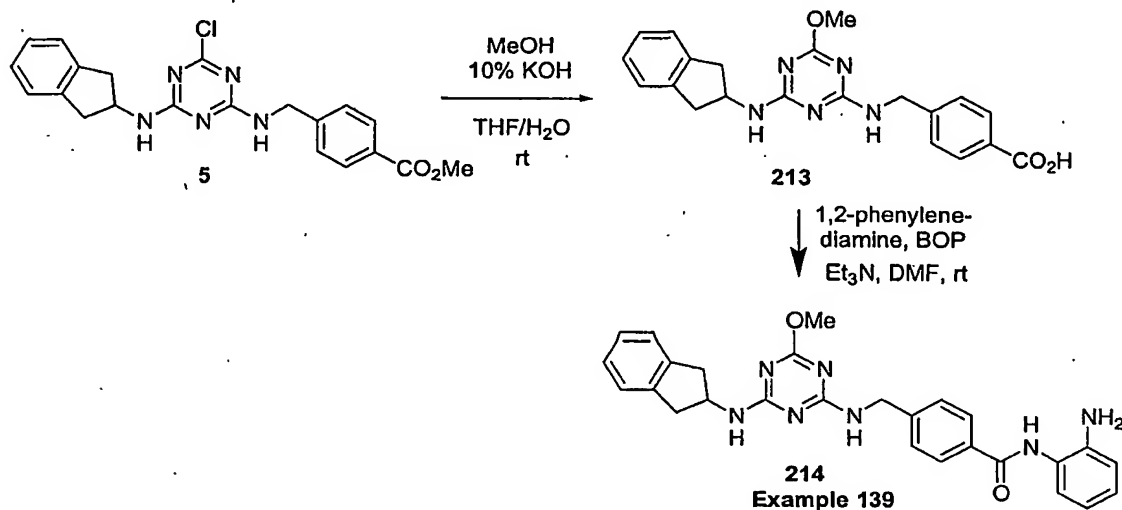
[0272] In a 75ml sealed flask, a stirred suspension of 2-chloro-4,6-dimethoxy-1,3,5-triazine (540 mg, 3.08 mmol), methyl 4-(aminomethyl)benzoate.HCl 2 (689 mg, 3.42 mmol), $i\text{-Pr}_2\text{NEt}$ (1.49 ml, 8.54 mmol) in anhydrous THF (30 ml) was warmed at 80°C for 5 h. Then, the reaction mixture was allowed to cool to room temperature, poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/ CH_2Cl_2 : 10/90 \rightarrow 30/70) to afford the title compound 211 (870 mg, 2.86 mmol, 93% yield) as a white solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm): AB system ($\delta_{\text{A}} = 8.01$, $\delta_{\text{B}} = 7.39$, $J_{\text{AB}} = 8.5$ Hz, 4H), 6.08-6.00 (m, 1H), 4.73 (d, $J = 6.3$ Hz, 2H), 3.95 (s, 6H), 3.92 (s, 3H).

[0273] The title compound 212 was obtained from 211 in 2 steps following the same procedure as Example 1, steps 4 and 5. ^1H NMR (300 MHz, acetone- d_6 + \sum DMSO- d_6) δ (ppm): 9.58 (bs, 1H), 8.27 (t, $J = 6.3$ Hz, 1H), AB system ($\delta_{\text{A}} = 8.04$, $\delta_{\text{B}} = 7.53$, $J_{\text{AB}} = 8.4$ Hz, 4H), 7.31 (d, $J = 6.9$ Hz, 1H), , 7.02 (td, $J = 7.6$, 1.6 Hz, 1H), 6.88 (dd, $J = 7.9$, 1.4 Hz, 1H), 6.68 (td, $J = 7.6$, 1.4 Hz, 1H), 4.86-4.78

(m, 2H), 4.69 (d, $J = 6.3$ Hz, 2H), , 3.90 and 3.89 (2s, 6H). HRMS (calc.): 380.1597, (found): 380.1601.

Step 2: *N*-(2-Amino-phenyl)-4-[(4,6-dimethoxy-[1,3,5]-triazin-2-yl-amino)-methyl]-benzamide (212)

Scheme 28



Example 139

Step 1: 4-[(6-(2-Indanyl-amino)-4-methoxy-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic acid (213)

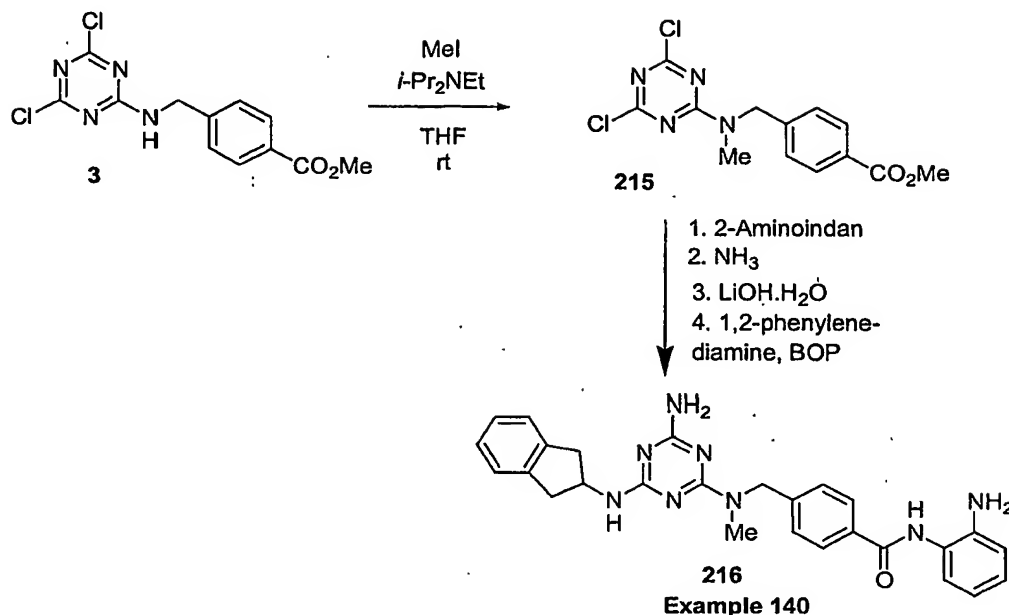
[0274] To a stirred solution at room temperature of 5 (300 mg, 0.73 mmol) in a mixture of MeOH/THF (10 ml/5 ml) was added an aqueous solution of KOH (10%, 5 ml). After 3 days, the reaction mixture was concentrated on the rotavap, diluted in water and acidified with 1N HCl until pH 5-6 in order to get a white precipitate. After 15 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound 213 (282 mg, 0.72 mmol, 98% yield) as a white solid. MS: $m/z = 392.1$ [MH] $^{+}$.

Step 2: *N*-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-methoxy-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide (214)

[0275] The title compound 214 was obtained from 213 in one step following the same procedure as Example 1, step 5. ^1H NMR (300 MHz, acetone- d_6 + ϵ DMSO- d_6) δ (ppm): mixture of rotamers, 9.69-9.53 (m, 1H), AB system ($\delta_A = 8.04$, $\delta_B = 7.52$, $J_{AB} = 7.8$ Hz, 4H), 7.80-7.60 (m, 1H), 7.45-7.10 (m, 6H), 7.01 (t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.68 (t, $J = 7.6$ Hz, 1H), 4.92-4.60 (m, 5H), 3.90-3.78 (m,

3H), 3.35-3.22 (m, 2H), 3.02-2.83 (m, 2H). HRMS (calc.): 481.2226, (found): 481.2231.

Scheme 29



Example 29

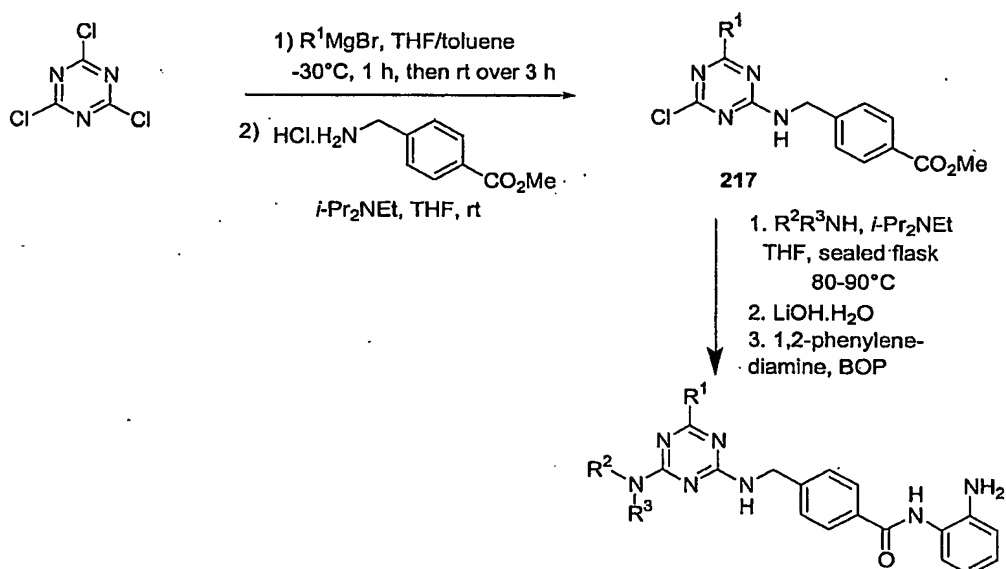
Step 1: Methyl 4-[(4,6-dichloro-[1,3,5]triazin-2-yl-N-methyl-amino)-methyl]-benzoic ester (216)

[0276] To a stirred suspension at room temperature of NaH (95%, 81 mg, 3.19 mmol) in anhydrous THF (10 ml) under nitrogen were successively added a solution of 3 (500 mg, 1.60 mmol) in anhydrous THF (10 ml) and MeI (298 μ l, 4.79 mmol). After 16 h, the reaction mixture was poured into a saturated aqueous solution of NH₄Cl, and diluted with AcOEt. After separation, the organic layer was successively washed with sat. NH₄Cl, H₂O and brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 10/90→20/80) to afford the title compound 215 (200 mg, 0.61 mmol, 38% yield) as a white crystalline solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm): AB system (δ_A = 8.04, δ_B = 7.31, J_{AB} = 8.2 Hz, 4H), 4.93 (s, 2H), 3.93 (s, 3H), 3.18 (s, 3H).

Step 2: 4-{[4-amino-6-(2-indanyl-amino)-[1,3,5]-triazin-2-yl-N-methyl-amino]-methyl}-N-(2-amino-phenyl)-benzamide (216)

[0277] The title compound 216 from 215 in 4 steps was obtained following the same procedure as Example 1, Pathway B steps 2-5. ^1H NMR (300 MHz, acetone- d_6) δ (ppm): 9.11 (bs, 1H), 8.03 (d, J = 8.0 Hz, 2H), 7.43 (bs, 2H), 7.33 (d, J = 7.7 Hz, 1H),), 7.28-7.09 (m, 4H), 7.04 (td, J = 7.6, 1.5 Hz, 1H), 6.90 (dd, J = 8.0, 1.4 Hz, 1H), 6.71 (td, J = 7.5, 1.3 Hz, 1H), 6.25-6.05 (m, 1H), 5.82 and 5.64 (2bs, 2H), 5.00-4.56 (m, 5H), 3.42-2.76 (m, 7H). HRMS (calc.): 480.2386, (found): 480.2377.

Scheme 30



Example 141 218: $\text{R}^1 = \text{Me}$, $\text{R}^2\text{R}^3\text{N} = 2\text{-indanyl-amino}$

Example 141:

Step 1: Methyl 4-[(4-chloro-6-methyl-[1,3,5]triazin-2-yl-amino)-methyl]-benzoic ester (217)

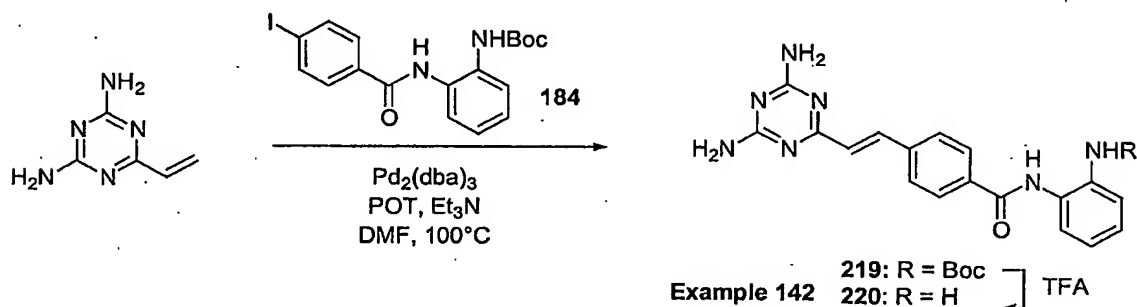
[0278] To a stirred solution at -30°C of cyanuric chloride 1 (2.00 g, 10.85 mmol) in anhydrous THF (100 ml) under nitrogen was slowly added a solution of MeMgBr (17 ml, 23.86 mmol, 1.4 M in anhydrous THF/toluene). After 1 h, the reaction mixture was allowed to warm to room temperature over 3 h. Then, methyl 4-(aminomethyl)benzoate.HCl 2 (2.08 g, 10.30 mmol) and $i\text{-Pr}_2\text{NEt}$ (3.78 ml, 21.69 mmol) were added, respectively. After 18 h, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt . After separation, the organic layer was

successively washed with sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{AcOEt}/\text{CH}_2\text{Cl}_2$: 10/90 \rightarrow 15/85) to afford the title compound 217 (780 mg, 2.67 mmol, 25% yield) as a yellow powder. ^1H NMR (300 MHz, CDCl_3) δ (ppm): mixture of rotamers, 2 AB system ($\delta_{\text{A}} = 8.03$, $\delta_{\text{A}'} = 8.02$, $\delta_{\text{B}} = 7.39$, $\delta_{\text{B}'} = 7.38$, $J = 8.5$ Hz, 4H), 6.28-6.08 (2 m, 1H), 4.76 and 4.74 (2d, $J = 6.3$ Hz, 2H), 3.92 (s, 3H), 2.46 and 2.42 (2s, 3H).

Step 2: *N*-(2-amino-phenyl)-4-{[6-(2-indanyl-amino)-4-methyl-[1,3,5]-triazin-2-yl-amino]-methyl}-benzamide (218)

[0279] The title compound 218 was obtained from 217 in 3 steps following the same procedure as Example 1, steps 3-5. ^1H NMR (300 MHz, acetone- d_6 + Σ DMSO- d_6) δ (ppm): mixture of rotamers, 9.62-9.50 (m, 1H), 8.04 (d, $J = 8.0$ Hz, 2H), 7.68-7.37 (m, 3H), 7.33 (d, $J = 7.7$ Hz, 1H), 7.28-7.07 (m, 5H), 7.02 (t, $J = 7.4$ Hz, 1H), 6.89 (d, $J = 7.9$ Hz, 1H), 6.69 (t, $J = 7.4$ Hz, 1H), 4.92-4.60 (m, 5H), 3.35-3.10 (m, 2H), 3.02-2.82 (m, 2H), 2.25-2.12 (m, 3H).

Scheme 31



Example 142

Step 1: (2-{4-[2-(4,6-Diamino-[1,3,5]triazin-2-yl)-vinyl]-benzoylamino}-phenyl)-carbamic tert-butyl ester (219)

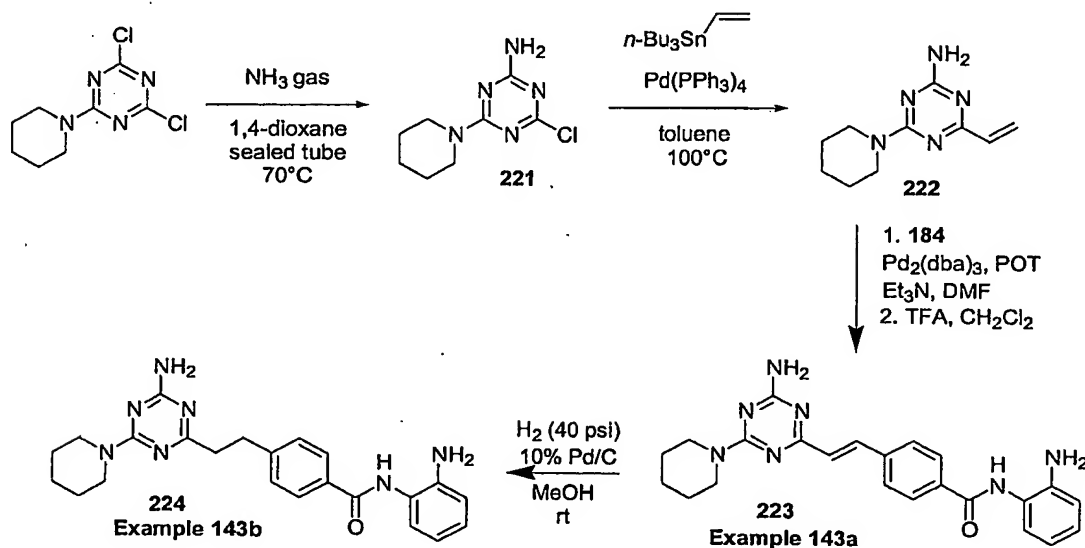
[0280] To a degazed solution of 184 (40 mg, 0.091 mmol) and 2-vinyl-4,6-diamino-1,3,5-triazine (11 mg, 0.083 mmol) in dry DMF (1 mL) was added tri-*o*-tolylphosphine (POT) (1.5 mg, 0.005 mmol) followed by Et_3N (46 μL , 0.33 mmol) and tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.0025 mmol). The solution was heated at 100°C for 16h. Then, DMF was removed under reduced pressure. The reaction mixture was partitioned between AcOEt and a solution of sat. NH_4Cl . After separation, the organic

layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$: 5/95) to afford the title compound **219** (25 mg, 0.056 mmol, 67% yield). ^1H NMR (300 MHz, Acetone- d_6) δ (ppm): 8.27 (s, 1H), 8.06 (d, J = 8.1 Hz, 2H), 7.96 (d, J = 15.9 Hz, 1H), 7.79 (d, J = 8.1 Hz, 2H), 7.76-7.69 (m, 1H), 7.62-7.55 (m, 1H), 7.26-7.15 (m, 2H), 6.90 (d, J = 15.9 Hz), 6.21 (s, 4H), 1.50 (s, 9H).

Step 2: *N*-(2-Amino-phenyl)-4-[2-(4,6-diamino-[1,3,5]triazin-2-yl)-vinyl]-benzamide (**220**)

[0281] To a stirred solution at room temperature of **219** (25 mg, 0.056 mmol) in CH_2Cl_2 (1.5 mL) was added TFA (0.3 mL, 4.3 mmol). After 30 min, a solution of sat. NaHCO_3 was slowly added until pH 8 is reached, CH_2Cl_2 was removed under reduced pressure, AcOEt was added, and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel ($\text{MeOH}/\text{CH}_2\text{Cl}_2$: 10/90) to afford the title compound **220** (19 mg, 0.054 mmol, 98% yield). ^1H NMR: (300 MHz, acetone- d_6) δ (ppm): 8.33, 8.13 (2d, J = 7.5 Hz, 1H), 8.22 (d, J = 15.9 Hz, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.38-6.96 (m, 2H), 7.03 (d, J = 15.9 Hz, 1H), 6.94-6.62 (m, 2H).

Scheme 32



Example 143a

Step 1: 2-Amino-4-chloro-6-piperidin-1-yl-[1,3,5]triazin (221)

[0282] Ammonia was bubbled for 5 min in a solution of 2,4-dichloro-6-piperidin-1-yl-[1,3,5]triazine (500 mg, 2.15 mmol) in dry 1,4-dioxane (20 mL). The solution was heated at 70°C for 16h in a sealed tube. The reaction mixture was allowed to cool to room temperature, and partitioned between AcOEt and a solution of sat. NH₄Cl. After separation, the organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to afford the title compound 221 (453 mg, 2.12 mmol, 98% yield). LRMS: [MH]⁺ = 214.1.

Step 2: 2-Amino 4-piperidin-1-yl-6-vinyl-[1,3,5]triazin (222)

[0283] To a solution of 221 (358 mg, 1.68 mmol) in dry toluene (7 mL) was added tributyl(vinyl)tin (514 μ L, 1.76 mmol) followed by Pd(PPh₃)₄ (97 mg, 0.084 mmol) and the reaction mixture was heated at 100°C for 16h in a sealed tube. Then, the reaction mixture was allowed to cool to room temperature, concentrated, and purified directly by flash chromatography on silica gel (AcOEt/hexane: 10/90→30/70) to afford the title compound 222 (containing tributyltin chloride).

Steps 3: N-(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-vinyl]-benzamide (223)

[0284] The title compound 223 was obtained from 222 in 2 steps following the same procedure as in scheme 31, steps 1 and 2. ¹H NMR: (300 MHz, DMSO-d₆) δ (ppm): 9.69 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.87 (d, J = 16.0 Hz, 1H), 7.80 (d, J = 7.5 Hz, 2H), 7.18 (d, J = 7.5 Hz, 1H), 7.04-6.92 (m, 1H), 6.91 (d, J = 16 Hz, 1H), 6.85-6.68 (m, 3H), 6.60 (t, J = 7.2 Hz, 1H), 4.93 (s, 2H), 3.77 (s, 4H), 1.63 (s, 2H), 1.52 (s, 4H).

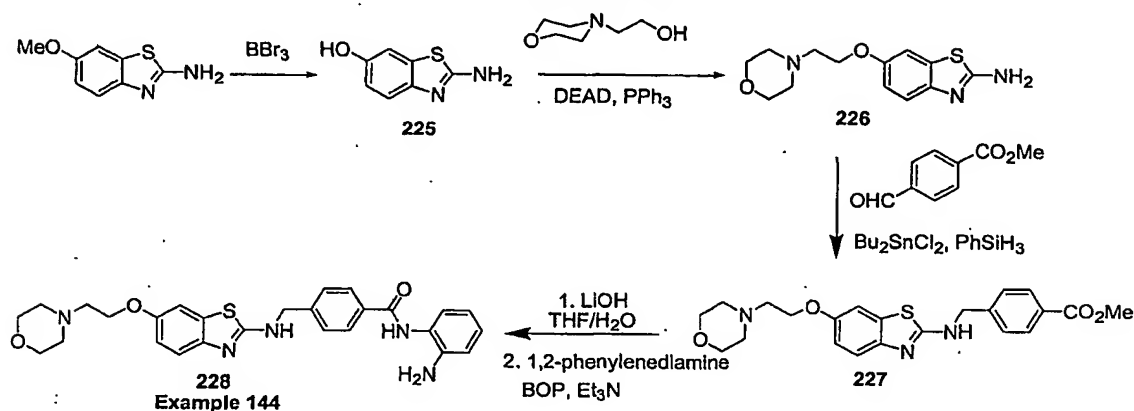
Example 143b

Step 4: N-(2-Amino-phenyl)-4-[2-(4-amino-6-piperidin-1-yl-[1,3,5]triazin-2-yl)-ethyl]-benzamide (224)

[0285] To a solution of 223 (18 mg, 0.043 mmol) in MeOH (5 mL) was added 10% Pd/C (10 mg, 0.021 mmol). The reaction mixture was shaken under a pressure of H₂ (40 psi) at room temperature for 16 h using an hydrogenation apparatus. Then, the reaction mixture was purged with N₂, filtered through celite, and concentrated. The crude residue was then purified by flash chromatography on silica gel (MeOH/CH₂Cl₂:

2/98→4/96) to afford the title compound **224** (10 mg, 0.024 mmol, 56% yield). ^1H NMR (300 MHz, CDCl_3 - CD_3OD) δ (ppm): 7.82 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 7.0 Hz, 1H), 6.89-6.79 (m, 2H), 7.80-6.90 (m, 1H), 3.76 (s, 4H), 3.13 (t, J = 8.1 Hz, 2H), 2.88 (t, J = 8.1 Hz, 2H), 1.90-1.40 (m, 10H).

Scheme 33



Example 144

Step 1: 2-Amino-benzothiazol-6-ol (225):

[0286] A suspension of 2-amino-6-methoxybenzothiazole (5.00 g, 27.8 mmol) in dichloromethane (70 mL) was cooled to 0°C under nitrogen and boron tribromide (3.93 mL, 41.6 mmol) was added dropwise. The light yellow mixture was stirred for 3 h, allowing to warm-up slowly from 0°C to 10°C. The reaction was slowly quenched by dropwise addition of methanol and after stirring overnight at room temperature, the white solid was collected by filtration (6.04 g, 88% yield). This hydrobromic salt was dissolved in water, washed with ethyl acetate, and neutralized with a saturated aqueous solution of NaHCO_3 . The resulting crystals were collected by filtration and dried in the oven at 135°C for 1h to afford the title compound **225** as colorless crystals (3.63 g, 79% yield). ^1H NMR: (CD_3OD) δ (ppm): 7.27 (d, J =8.8 Hz, 1H), 7.08 (d, J =2.2 Hz, 1H), 6.80 (dd, J =8.4, 2.2 Hz, 1H).

Step 2: 6-(2-Morpholin-4-yl-ethoxy)-benzothiazol-2-ylamine (226)

[0287] To a solution of benzothiazole **225** (3.62 g, 21.8 mmol) in THF at room temperature under nitrogen, were successively added 4-(2-hydroxyethyl)morpholine (3.17 mL, 26.1 mmol), triphenylphosphine (7.43 g, 28.3 mmol) followed by a dropwise addition of diethyl

azodicarboxylate (4.46 mL, 28.3 mmol). The solution was stirred for 3.5 h and THF was partially removed *in vacuo*. The mixture was partitioned between ethyl acetate and H₂O. The combined organic layers were extracted with 1N HCl. The combined acidic extracts were neutralized using a saturated aqueous solution of NaHCO₃ and the precipitate was dissolved with ethyl acetate. These combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The filtrate was concentrated to afford the title compound 226 (5.83 g, 96% yield) as a light yellow oil. ¹H NMR:

(Acetone-d₆) δ (ppm): 7.37 (d, J=8.8 Hz, 1H), 7.34 (d, J=2.6 Hz, 1H), 6.94 (dd, J=8.8, 2.6 Hz, 1H), 6.60 (bs, 2H), 4.19 (t, J=6.2 Hz, 2H), 3.70-3.67 (m, 4H), 2.90 (s, 2H), 2.81 (t, J=6.2 Hz, 2H), 2.62-2.58 (m, 4H).

Step 3: 4-{[6-(2-Morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzoic acid methyl ester (227):

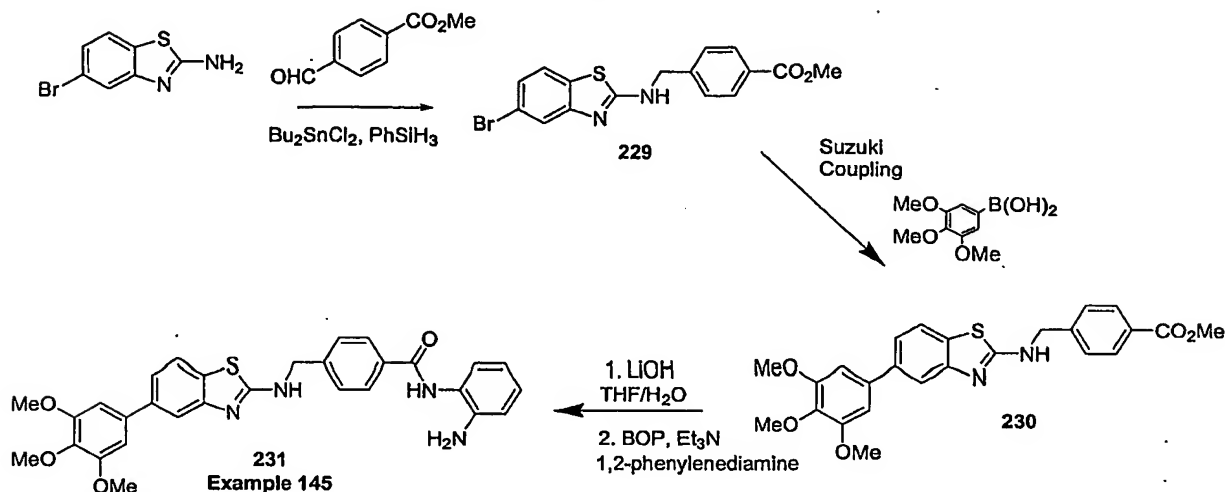
[0288] To a round-bottom flask containing benzothiazole 226 (5.80 g, 20.8 mmol) was added methyl 4-formylbenzoate (5.11 g, 31.1 mmol), followed by THF (8 mL), dibutyltin dichloride (315 mg, 1.04 mmol) and dropwise addition of phenylsilane (3.24 mL, 31.1 mmol). The resulting mixture was stirred overnight at room temperature under nitrogen. The mixture was diluted in ethyl acetate and filtered. The filtrate was partitioned between ethyl acetate and water and the combined organic layers were washed with 1N HCl. The combined acidic layers were neutralized using a saturated aqueous solution of NaHCO₃ and the precipitate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The resulting crude was purified by flash chromatography using MeOH/CHCl₃ (10:90) to afford 227 (3.69 g, 42% yield). ¹H NMR: (Acetone-d₆) δ (ppm): 8.04 (d, J=8.5 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.41 (d, J=8.8 Hz, 1H), 7.34 (d, J=2.5 Hz, 1H), 6.94 (dd, J=8.5, 2.7 Hz, 1H), 4.50 (t, J=5.5 Hz, 2H), 3.86 (s, 3H).

Step 4: N-(2-Amino-phenyl)-4-{[6-(2-morpholin-4-yl-ethoxy)-benzothiazol-2-ylamino]-methyl}-benzamide (228):

[0289] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 228 was obtained (958 mg, 46%) as a colorless solid. ¹H NMR: (CD₃OD) δ (ppm): 8.04 (d, J=8.2 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 7.40 (d, J=8.8 Hz, 1H), 7.31 (d, J=2.5 Hz, 1H), 7.25 (d, J=7.4 Hz, 1H), 7.15

(t, J=7.4 Hz, 1H), 6.97 (dd, J=8.8, 2.5 Hz, 2H), 6.84 (t, J=7.4 Hz, 1H), 4.78 (s, 2H), 4.21 (t, J=5.2 Hz, 2H), 3.81-3.77 (m, 4H), 2.87 (t, J=5.5, 2H), 2.69-3.66 (m, 4H).

Scheme 34



Example 145

Step 1: 4-[(5-Bromo-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (229):

[0290] Following the procedure described in Example 144, step 3, but substituting the 2-amino-6-bromobenzothiazole for 226, the title compound 229 was obtained in 56% yield. ^1H NMR: ($\text{DMSO}-d_6$) δ (ppm): 8.78 (t, J= 5.9 Hz, 1H), 8.01 (d, J= 8.2 Hz, 2H), 7.99 (s, 1H), 7.56 (d, J= 8.2 Hz, 2H), 7.43-7.34 (m, 2H), 4.74 (d, J= 5.9 Hz, 2H), 3.90 (s, 3H).

Step 2: 4-{[5-(3,4,5-Trimethoxy-phenyl)-benzothiazol-2-ylamino]-methyl}-benzoic acid methyl ester (230):

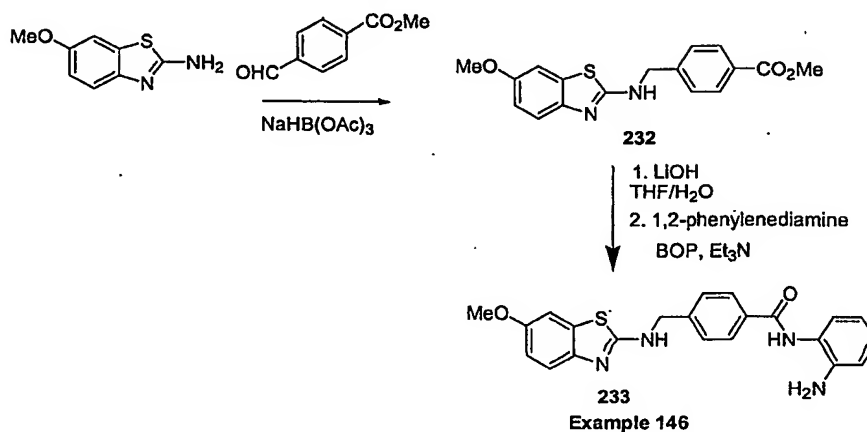
[0291] Following the procedure described in Example 15, step 1, but substituting 229 for 140, the title compound 230 was obtained in 44% yield as colorless crystals. ^1H NMR: ($\text{DMSO}-d_6$) δ (ppm): 8.73 (t, J=5.7 Hz, 1H), 8.11 (d, J=1.8 Hz, 1H), 8.02 (d, J=8.4 Hz, 2H), 7.63-7.57 (m, 3H), 7.48 (d, J=8.4 Hz, 1H), 6.97 (s, 2H), 4.77 (d, J=5.7 Hz, 2H), 3.92 (m, 6H), 3.90 (s, 3H), 3.74 (s, 3H).

Step 3: N-(2-Amino-phenyl)-4-{[5-(3,4,5-trimethoxy-phenyl)-benzothiazol-2-ylamino]-methyl}-benzamide (231):

[0292] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 231

was obtained in 69% yield. ^1H NMR: (Acetone- d_6) δ (ppm): 8.31 (d, $J=7.9$ Hz, 2H), 8.20 (d, $J=7.5$ Hz, 1H), 8.13 (s, 1H), 7.73-7.58 (m, 3H), 7.63 (d, $J=7.5$ Hz, 2H), 7.48-7.43 (m, 2H), 7.05 (s, 2H), 4.98 (s, 2H), 4.00 (s, 6H), 3.84 (s, 3H).

Scheme 35



Example 146

Step 1: 4-[(6-Methoxy-benzothiazol-2-ylamino)-methyl]-benzoic acid methyl ester (232):

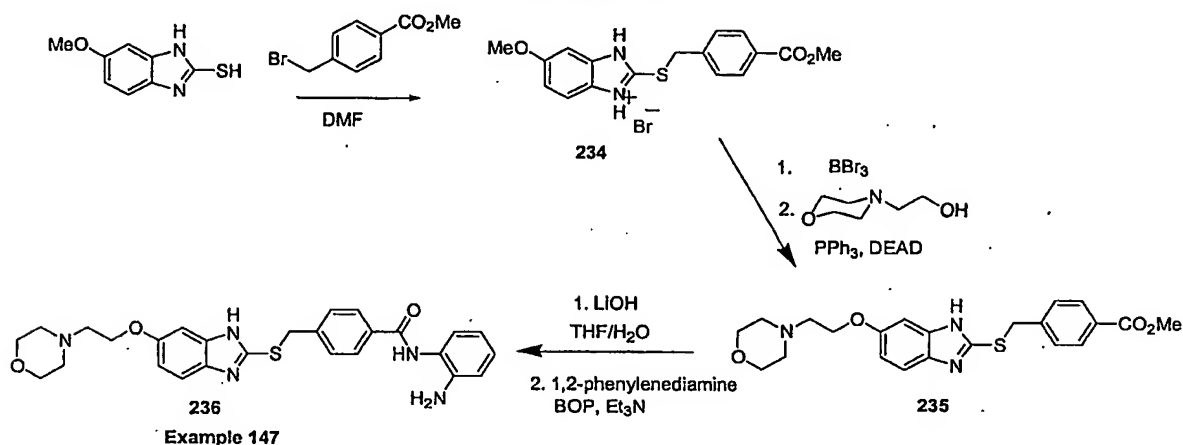
[0293] To a solution of 2-amino-6-methoxybenzothiazole (2.00 g, 11.1 mmol) in a mixture of dichloroethane (20 mL) and THF (20 mL), were successively added methyl 4-formylbenzoate (1.82 g, 11.1 mmol), sodium triacetoxyborohydride (3.53 g, 16.7 mmol) and acetic acid (1.27 mL, 22.2 mmol). The mixture was stirred over 2 days and was quenched by adding aqueous saturated solution of NaHCO_3 . The mixture was poured in a separating funnel containing water and was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude material was purified by flash chromatography using EtOAc /hexane (20:80 to 30:70) to afford the title compound 232 (1.85g, 51% yield). ^1H NMR: (Acetone- d_6) δ (ppm): 8.04 (d, $J=8.5$ Hz, 2H), 7.65 (d, $J=8.8$ Hz, 2H), 7.41 (d, $J=8.8$ Hz, 1H), 7.34 (d, $J=2.5$ Hz, 1H), 6.94 (dd, $J=8.5, 2.7$ Hz, 1H), 4.50 (t, $J=5.5$ Hz, 2H), 3.86 (s, 3H).

Step 2: N-(2-Amino-phenyl)-4-[(6-methoxy-benzothiazol-2-ylamino)-methyl]-benzamide (233):

[0294] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 233 was obtained in 19% yield as a light beige solid. ^1H NMR: (DMSO- d_6) δ

(ppm): 9.68 (s, 1H), 8.44 (t, J=5.8 Hz, 1H), 8.00 (d, J=8.2 Hz, 2H), 7.55 (d, J=8.2 Hz, 2H), 7.39 (d, J=2.7 Hz, 1H), 7.34 (d, J=8.8 Hz, 1H), 7.21 (d, J=6.6 Hz, 1H), 7.05 (t, J=6.3 Hz, 1H), 7.00 (d, J=1.4 Hz, 1H), 6.88 (dd, J=8.8, 2.7 Hz, 1H), 6.86 (dd, J=8.0, 1.4 Hz, 1H), 6.65 (td, J=7.4, 1.4 Hz, 1H), 4.95 (s, 2H), 4.70 (d, J=5.8 Hz, 2H), 3.79 (s, 3H).

Scheme 36



Example 147

Step 1: 4-(6-Methoxy-1H-benzimidazol-2-ylsulfanylmethyl)-benzoic acid methyl ester hydrobromide (234):

[0295] To a solution of methyl 4-(bromomethyl)benzoate (2.51g, 11.0 mmol) in DMF (50 mL) was added 5-methoxy-2-benzimidazolethiol (1.98g, 11.0 mmol). The mixture was stirred at room temperature for 24 h and the solvent was evaporated in vacuo. The residue was suspended in ethyl acetate and the hydrobromide salt was collected by filtration to afford the title compound 234 (4.10g, 91% yield) as a colorless solid. ¹H NMR: (DMSO-d₆) δ (ppm): 7.90 (d, J= 8.2 Hz, 2H), 7.55 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 1H), 7.03 (s, 1H), 6.94 (d, J= 8.2 Hz, 1H), 4.65 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H).

Step 2: 4-[6-(2-Morpholin-4-yl-ethoxy)-1H-benzimidazol-2-ylsulfanylmethyl]-benzoic acid methyl ester (235):

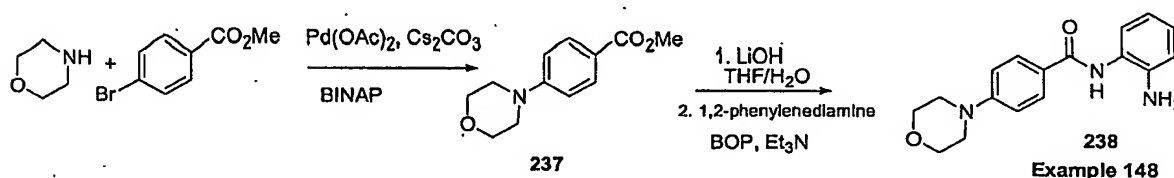
[0296] Following the procedure described in Example 144, step 1, 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound 235 was obtained in 37% yield. ¹H NMR: (CDCl₃) δ (ppm): 8.04-8.00 (m, 2H), 7.77-7.72 (m, 1H), 7.69-7.59 (m, 1H), 7.56-7.49 (m, 2H), 6.96-6.90 (m, 1H), 4.68

(s, 2H), 4.31-4.16 (m, 4H), 3.97 (s, 3H), 3.98-3.91 (m, 2H), 3.82-3.72 (m, 2H), 2.75-2.47 (m, 4H):

Step 3: N-(2-Amino-phenyl)-4-[6-(2-morpholin-4-yl-ethoxy)-1H-benzoimidazol-2-ylsulfanylmethyl]-benzamide (236):

[0297] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 236 was obtained in 11% yield. ¹H NMR: (CD₃OD) δ (ppm): 7.89 (d, J= 8.2 Hz, 2H), 7.45 (d, J= 8.2 Hz, 2H), 7.28 (d, J= 8.5 Hz, 1H), 7.19-7.06 (m, 3H), 6.93-6.79 (m, 3H), 4.55 (s, 2H), 4.18 (t, J= 6.3 Hz, 2H), 3.65-3.62 (m, 4H), 2.51 (t, J= 6.6 Hz, 2H), 2.46-2.42 (m, 4H).

Scheme 37



Example 148

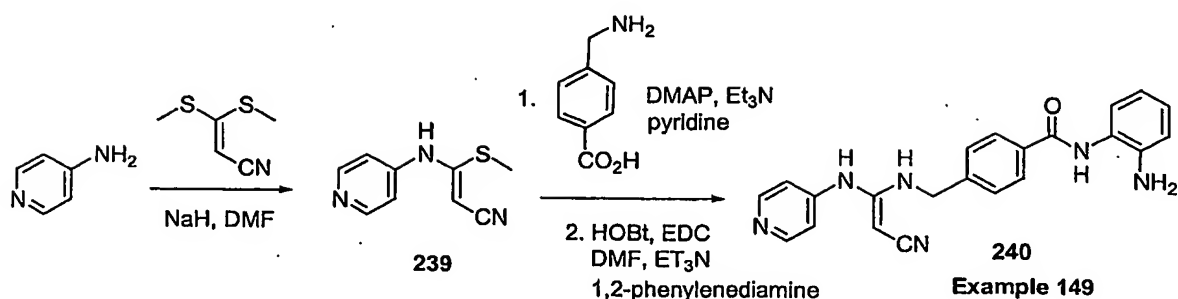
Step 1: 4-Morpholin-4-yl-benzoic acid methyl ester (237):

[0298] A flame-dried pressure vessel was charged with cesium carbonate (912 mg, 2.80 mmol) and toluene (8 mL) and the flasked was purged with nitrogen. Palladium acetate (9.0 mg, 0.004 mmol) and *rac*-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (37 mg, 0.06 mmol). The mixture was degassed and heated at 100°C for 18 h. It was allowed to cool to room temperature and was filtered through celite, rinsed with ethyl acetate and partitioned between ethyl acetate and water. The organic layer was washed with a saturated solution of NaHCO₃, brine, dried over MgSO₄ and concentrated *in vacuo* to afford the title compound 237 (443 mg, 100% yield). ¹H NMR: (CDCl₃) δ (ppm): 8.02 (d, J=9.2 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 3.95 (s, 4H), 3.92 (s, 3H), 3.38-3.35 (m, 4H).

Step 2: N-(2-Amino-phenyl)-4-morpholin-4-yl-benzamide (238):

[0299] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 238 was obtained in 33 % yield. ¹H NMR: (DMSO-d₆) δ (ppm): 7.20 (d, J= 7.9 Hz, 1H), 7.07 (d, J= 8.8 Hz, 2H), 7.01 (t, J= 7.0 Hz, 1H), 6.83 (d, J= 7.9 Hz, 1H), 6.65 (t, J= 7.5 Hz, 1H), 4.90 (s, 2H), 3.81-3.79 (m, 4H), 3.32-3.28 (m, 4H).

Scheme 38



Example 149

Step 1: 3-Methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (239)

[0300] To a solution of pyridin-4-ylamine (1.0 g, 11.0 mmol) and 3,3-Bis-methylsulfanyl-acrylonitrile (2.05 g, 12.6 mmol) in DMF at room temperature, was added powdered 4A molecular sieves. The mixture was stirred for 1 hr. Subsequently the mixture was cooled to 0 °C, 60% NaH dispersion in oil (0.92 g, 23.0 mmol) was added portionwise over 1 hr. and it was stirred at 0 °C for an additional 2 hrs. The cold bath was removed and the mixture was stirred at room temperature for 20 hrs. DMF was removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 25% MeOH/EtOAc) to afford the desired product as an off-white solid (1.9 g, 89%).

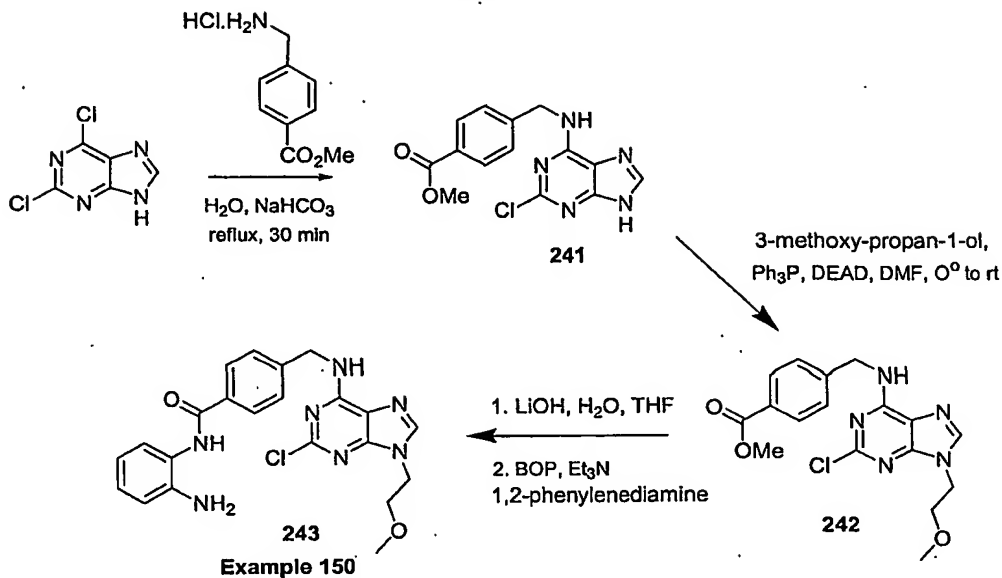
Step 2: N-(2-Amino-phenyl)-4-{[2-cyano-1-(pyridin-4-ylamino)-vinylamino]-methyl}-benzamide (240)

[0301] To a mixture of 3-methylsulfanyl-3-(pyridin-4-ylamino)-acrylonitrile (0.2 g, 1.0 mmol), 4-aminomethyl-benzoic acid (0.173 g, 1.14 mmol), DMAP (1 mg) and Et₃N (0.14 ml, 1.0 mmol) was added dry pyridine (0.5 ml). The resulting stirring mixture was heated to 55 °C for 4.5 hrs., additional Et₃N (0.14 ml) was added and mixture was heated from 75 °C to 90 °C over a period of ~30 hrs. When the reaction was complete, pyridine was partially removed in vacuo and the crude was purified by column chromatography (gradient of EtOAc to 20% MeOH/EtOAc) to afford the desired product as an off-white solid (130 mg, 44%).

[0302] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 240 was obtained in 33 % yield. ¹H NMR: (300 MHz, DMSO-d₆) δ (ppm): 9.69 (br, 2H), 8.48 (br, 3H), 8.03 (d, J = 7.9 Hz, 2H), 7.51

(d, $J = 8.4$ Hz, 2H), 7.29 (br, 2H), 7.23 (d, $J = 7.9$ Hz, 1H), 7.03 (t, $J = 7.0$ Hz, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 6.65 (t, $J = 7.3$ Hz, 1H), 4.96 (br, 2H), 4.62 (d, $J = 5.7$ Hz, 2H).

Scheme 39



Example 150

Step 1: 4-[(2-Chloro-9H-purin-6-ylamino)-methyl]-benzoic acid methyl ester (241)

[0303] A suspension of 2,6-dichloro-9H-purine (1 g, 5.29 mmol), 4-aminomethyl-benzoic acid methyl ester hydrochloride (1.2 equiv., 1.28 g) and NaHCO₃ (2.1 equiv., 935 mg) in water was heated at 100°C. The homogeneous solution thus formed was refluxed 30 min. The resulting white precipitate was filtered, washed with cold water and dried under vacuum giving the title compound 241 (1 g, 3.14 mmol, 60%). LRMS calc:317.7, found: 318.3 (MH)⁺.

Step 2: 4-[[2-Chloro-9-(2-methoxy-ethyl)-9H-purin-6-ylamino]-methyl]-benzoic acid methyl ester (242)

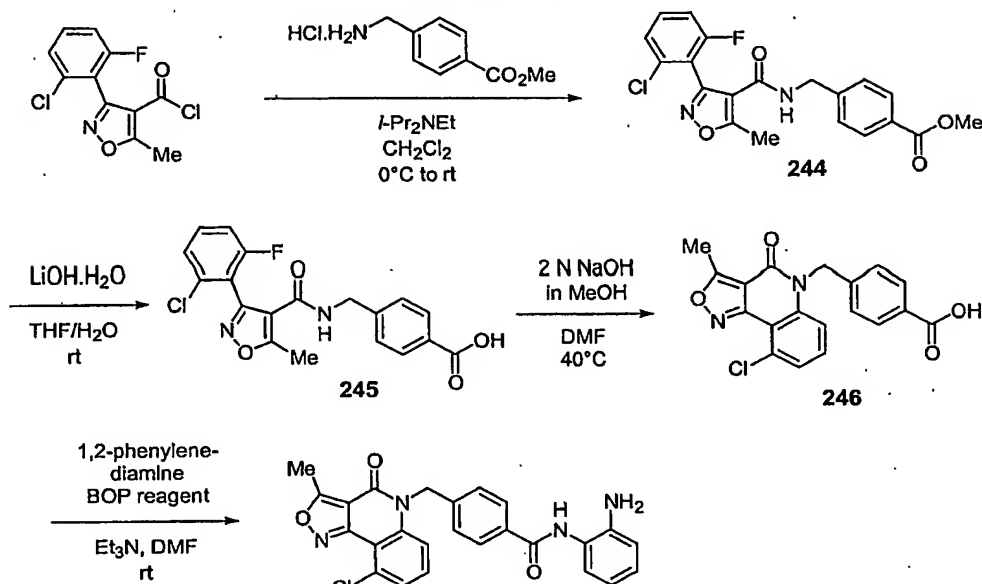
[0304] Following the procedure described in Example 144, step 2 but substituting the previous compound for 2-amino-6-methoxybenzothiazole, the title compound 242 was obtained in 41% yield.

Step 3: N-(2-Amino-phenyl)-4-[[2-chloro-9-(2-methoxy-ethyl)-9H-purin-6-ylamino]-methyl]-benzamide (243):

[0305] Following the procedure described in Example 1, step 4, 5 but substituting the previous compound for 6, the title compound 243

was obtained in 85% yield. ^1H NMR (CDCl_3) δ (ppm): 9.64 (s, 1H), 8.94 (bs, 1H), 8.18 (s, 1H), 7.96 (d, $J = 7.8$ Hz; 2H), 7.52 (d, $J = 7.8$ Hz, 2H), 7.21 (d, $J = 7.7$ Hz, 1H), 7.01 (dd, $J = 7.3, 8.0$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.62 (dd, $J = 7.3, 7.7$ Hz, 1H), 4.91 (bs, 2H), 4.78 (bs, 2H), 4.18 (m, 2H), 3.70 (m, 2H), 3.26 (s, 3H)

Scheme 40



247
Example 151.

Example 151

Step 1: Methyl-4-{[3-(2-chloro-6-fluorophenyl)-5-methyl-isoxazole-4-carbonyl]-amino-methyl}-benzoic acid ester (244)

[0306] To a stirred suspension at 0°C of methyl 4-(aminomethyl)benzoate.HCl 2 (809 mg, 4.01 mmol) in anhydrous CH_2Cl_2 (25 ml) under nitrogen were successively added *i*- Pr_2NEt (1.91 ml, 10.95 mmol) and 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl chloride (1.00 g, 3.65 mmol). After 45 min, the reaction mixture was allowed to warm up to room temperature for 3 h. Then, the reaction mixture was concentrated, diluted with AcOEt, and successively washed with sat. NH_4Cl , H_2O , sat. NaHCO_3 , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated to afford the title compound 244 (1.50 g, quantitative yield) as a colorless sticky foam. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.93 (d, $J = 7.9$ Hz, 2H), 7.46-7.35 (m, 1H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.15-7.05 (m, 3H), 5.49 (bs, 1H), 4.46 (d, $J = 5.7$ Hz, 2H), 3.92 (s, 3H), 2.80 (s, 3H).

Step 2: 4-{[3-(2-Chloro-6-fluoro-phenyl)-5-methyl-isoxazole-4-carbonyl]-amino-methyl}-benzoic acid (245)

[0307] To a stirred solution at room temperature of 244 (1.45 g, 3.60 mmol) in THF (20 ml) was added a solution of LiOH.H₂O (453 mg, 10.80 mmol) in water (20 ml). After 20 h, the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until pH 6 in order to get a white precipitate. After 10 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound 245 (1.23 g, 3.15 mmol, 88% yield) as a white solid. ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 8.69 (t, J = 5.9 Hz, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.70-7.58 (m, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.45-7.30 (m, 3H), 4.44 (d, J = 5.7 Hz, 2H), 2.72 (s, 3H).

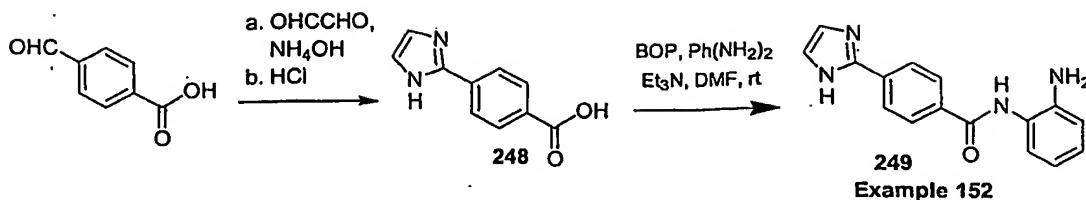
Step 3: 4-(9-Chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzoic acid (246)

[0308] To a stirred suspension at room temperature of 245 (795 mg, 2.05 mmol) in anhydrous DMF (10 ml) was added a solution of NaOH (409 mg, 10.22 mmol) in anhydrous MeOH (5.1 ml). Then, the reaction mixture was warmed up to 40°C. After 3 days, the reaction mixture was concentrated, diluted with water and acidified with 1N HCl until pH 5 in order to get a pale pinky precipitate. After 30 min, the suspension was filtered off and the cake was abundantly washed with water, and dried to afford the title compound 246 (679 mg, 1.84 mmol, 90% yield) as a pale pinky solid. ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): AB system (δ_A = 7.92, δ_B = 7.40, J = 8.4 Hz, 4H), 7.56 (t, J = 8.1 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 5.59 (bs, 2H), 2.95 (s, 3H).

Step 4: N-(2-Amino-phenyl)-4-(9-chloro-3-methyl-4-oxo-4H-isoxazolo[4,3-c]quinolin-5-ylmethyl)-benzamide (247)

[0309] The title compound 247 was obtained from 246 in one step following the same procedure as Example 1, steps 5. ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.65 (s, 1H), AB system (δ_A = 7.95, δ_B = 7.42, J = 8.1 Hz, 4H), 7.58 (t, J = 8.1 Hz, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 8.3 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 6.62 (t, J = 7.3 Hz, 1H), 5.61 (bs, 2H), 4.91 (s, 2H), 2.97 (s, 3H).

Scheme 41



Example 152

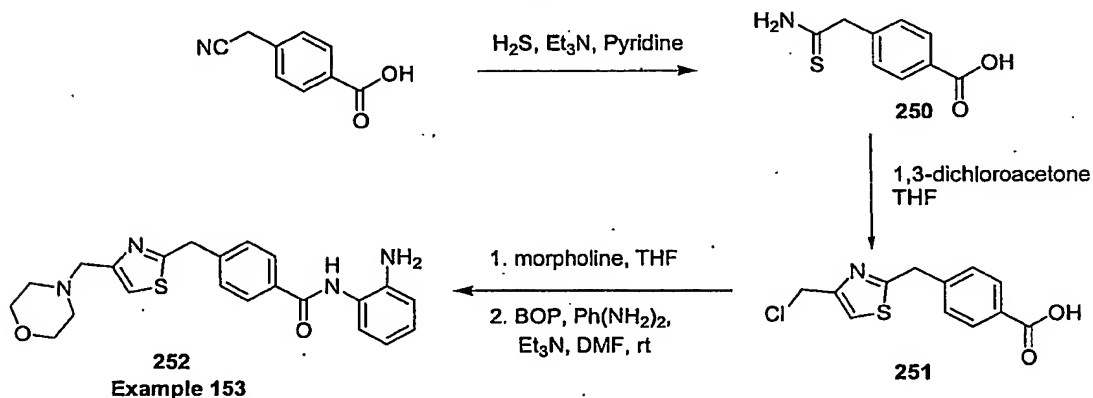
Step 1: 4-(1H-Imidazol-2-yl)-benzoic acid (248)

[0310] To a stirred solution of 4-formylbenzoic acid (2.00 g, 12.3 mmol) in ammonium hydroxide (9 ml) was added glyoxal (2.86 ml, 20.0 mmol). The reaction mixture was stirred 16 h at room temperature. 1N HCl was added to the reaction mixture to acidify to pH 5. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound 248 (2.08 g, 83%) as a white solid. LRMS: 188.1 (Calc.); 189.1 (found).

Step 2: N-(2-Amino-phenyl)-4-(1H-imidazol-2-yl)-benzamide (249)

[0311] The title compound 249 was obtained following the same procedure as Example 1, step 5. ^1H NMR (CDCl_3) δ (ppm): ^1H NMR: (DMSO) δ (ppm): 9.72 (bs, 1H), 8.07 (s, 4H), 7.26 (s, 2H), 7.18 (d, $J = 7.9$ Hz, 1H), 6.98 (dd, $J = 7.5, 7.5$ Hz, 1H), 6.79 (d, $J = 7.9$ Hz, 1H), 6.60 (dd, $J = 7.5, 7.5$ Hz, 1H). MS: (calc.) 278.1; (obt.) 279.1 (MH) $^+$.

Scheme 42



Example 153

Step 1: 4-Thiocarbamoylmethyl-benzoic acid (250)

[0312] To a stirred suspension of 4-cyanomethyl-benzoic acid (1.65 g, 10.24 mmol) and Et_3N (5 ml) in pyridine, H_2S was bubbled during 3 h. The reaction mixture was stirred 16 h at room temperature. Water

was then added to the reaction mixture which was agitated for 1 h before acidifying to pH 6 with 1M HCl. The solvent was evaporated and the residue was triturated 30 min. in water (20 ml) and filtered to obtain the title compound 250 (2.08 g, 83%) as a white solid. ¹H NMR (DMSO) δ (ppm): 12.85 (bs, 1H), 9.53 (bs, 1H), 9.43 (bs, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 3.88 (s, 2H).

Step 2: 4-(4-Chloromethyl-thiazol-2-ylmethyl)-benzoic acid (251)

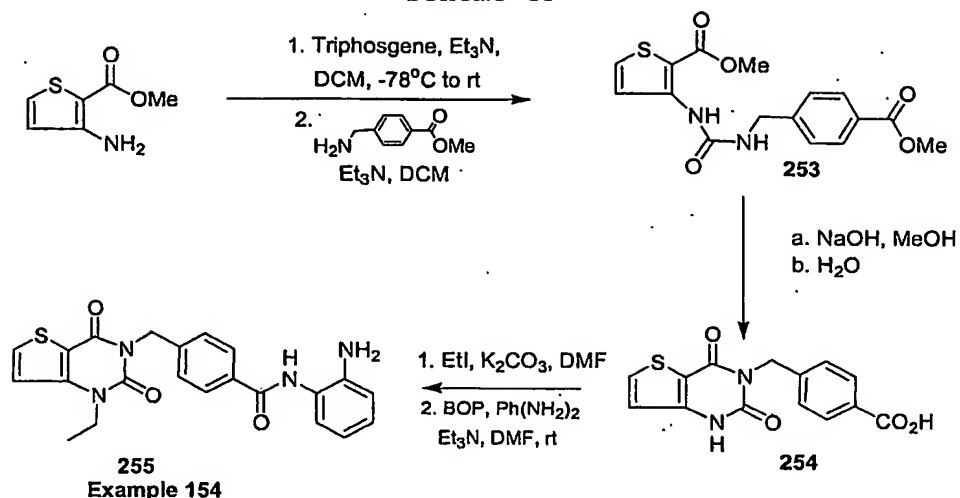
[0313] A solution of 250 (729 mg, 3.73 mmol) and 1,3-dichloroacetone (474 mg, 3.73 mmol) in THF (30 ml) was stirred at 40°C during 48h. The solvent was evaporated then the residue was dissolved in ethyl acetate, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (2-4% MeOH/CH₂Cl₂) to afford the title compound (827 mg, 83% yield) as a white solid. ¹H NMR (DMSO) δ (ppm): 12.93 (bs, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.46 (d, J = 8.1 Hz, 2H), 4.78 (s, 2H), 4.42 (s, 2H).

Step 3: N-(2-Amino-phenyl)-4-(4-morpholin-4-ylmethyl-thiazol-2-ylmethyl)-benzamide (252)

[0314] K₂CO₃ (599 mg, 4.33 mmol) was added to a solution of 251 (527 mg, 1.97 mmol) and morpholine (189 μl, 2.17 mmol) in THF (15 ml) was refluxed during 48h. The solvent was evaporated. The crude residue was purified by flash chromatography on silica gel (3-50% MeOH/CH₂Cl₂) to afford the title compound 252 (238 mg, 38% yield) as a pale yellow solid. LRMS: 318.2 (calc) 319.2 (found).

[0315] The title compound 252 was obtained following the same procedure as Example 1, step 5. ¹H NMR (DMSO) δ (ppm): 9.63 (bs, 1H), 7.94 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.33 (s, 1H), 7.15 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 7.7, 7.7 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.59 (dd, J = 8.1, 8.1 Hz, 1H), 4.90 (bs, 2H), 4.40 (s, 2H), 3.59-3.56 (m, 6H), 2.44-2.38 (m, 4H). LRMS: 408.2 (calc) 409.2 (found).

Scheme 43



Example 154

Step 1: Methyl 3-[3-(4-methoxycarbonyl-benzyl)-ureido]-thiophene-2-carboxylate (253)

[0316] The procedure described by Nakao (K. Nakao, R. Shimizu, H. Kubota, M. Yasuhara, Y. Hashimura, T. Suzuki, T. Fujita and H. Ohmizu; *Bioorg. Med. Chem.* 1998, 6, 849-868.) was followed to afford the title compound 253 (1.01 g, 91%) as a yellow solid. ¹H NMR (CDCl₃) δ (ppm): 9.55 (bs, 1H), 8.00-7.97 (m, 3H), 7.42-7.37 (m, 3H), 5.45 (t, J = 5.8 Hz, 1H), 4.52 (d, J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.82 (s, 3H).

Step 2: 4-(2,4-Dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzoic acid (254)

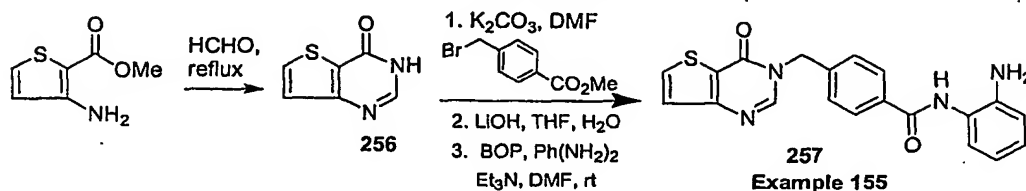
[0317] To a suspension of 253 (422 mg, 1.21 mmol) in MeOH (15 ml) was added NaOH (145 mg, 3.63 mmol). The reaction mixture was heated at 60°C during 16 h. Water (1 ml) was then added and the reaction mixture was stirred for 1 more hour. The solvent was evaporated and the residue was dissolved in water and acidified to pH 5 with HCl 1M. The precipitate was filtered to afford the desired compound 254 (348 mg, 95%) as a white solid. LRMS: 302.0 (Calc.); 303.0 (found).

Steps 3: N-(2-Amino-phenyl)-4-(1-ethyl-2,4-dioxo-1,4-dihydro-2H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (255)

[0318] The title compound 255 was obtained as a yellow solid (73%) following the same procedure as Example 99, step 2, 3, then followed by Example 1, step 5. ¹H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H, NH), 8.22 (d, J = 5.5 Hz, 1H, CH), 7.91 (d, J = 8.2 Hz, 2H, CH), 7.43-7.40 (m,

3H, CH), 7.15 (d, $J = 7.4$ Hz, 1H, CH), 6.96 (dd, $J = 7.6, 7.6$ Hz, 1H, CH), 6.77 (d, $J = 7.1$ Hz, 1H, CH), 6.59 (dd, $J = 7.4, 7.4$ Hz, 1H, CH), 5.17 (s, 2H, NCH_2), 4.88 (bs, 2H, NH_2) 4.09 (q, $J = 7.0$, 2H, CH_2), 1.22 (t, $J = 7.0$, 3H, CH_3). LRMS: 420.1 (calc.); 421.0 (found).

Scheme 44



Example 155

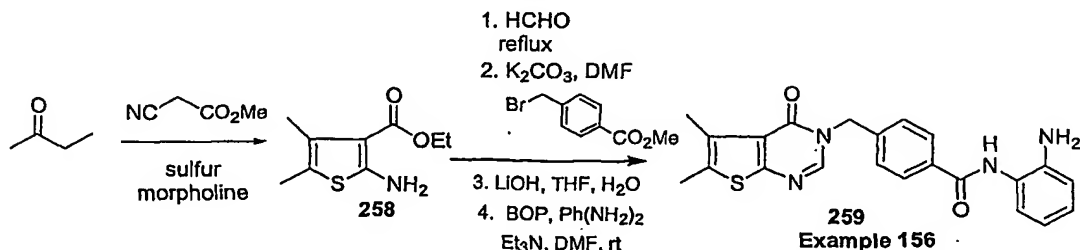
Step 1: 3H-Thieno[3,2-d]pyrimidin-4-one (256)

[0319] Methyl-3-amino-2-thiophene carboxylate (510 mg, 3.24 mmol) was dissolved in formamide (20 ml) and heated at 170°C 16h. The solvent was evaporated. The crude residue was then purified by flash chromatography on silica gel (2-4% MeOH/ CH_2Cl_2) to afford the title compound 256 (157 mg, 32% yield). LRMS: 152.0 (Calc.); 152.9 (found).

Step 2: N-(2-Aminophenyl)-4-(4-oxo-4H-thieno[3,2-d]pyrimidin-3-ylmethyl)-benzamide (257)

[0320] Following the procedure described in Example 85, step 1 but substituting the previous compound for 119, followed by Example 1, step 4, 5, the title compound 257 was obtained in 41% yield. ^1H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.70 (s, 1H), 8.22 (dd, $J = 5.2, 0.5$ Hz, 1H), 7.95 (d, $J = 8.2$ Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.44 (dd, $J = 5.2, 0.6$ Hz, 1H), 7.15 (d, $J = 7.7$ Hz, 1H), 6.96 (dd, $J = 6.9, 6.9$ Hz, 1H), 6.77 (d, $J = 7.1$ Hz, 1H), 6.58 (dd, $J = 7.0, 7.0$ Hz, 1H), 5.31 (s, 2H), 4.87 (bs, 2H). MS: 376.1 (calc.); 377.1 (found).

Scheme 45



Example 156

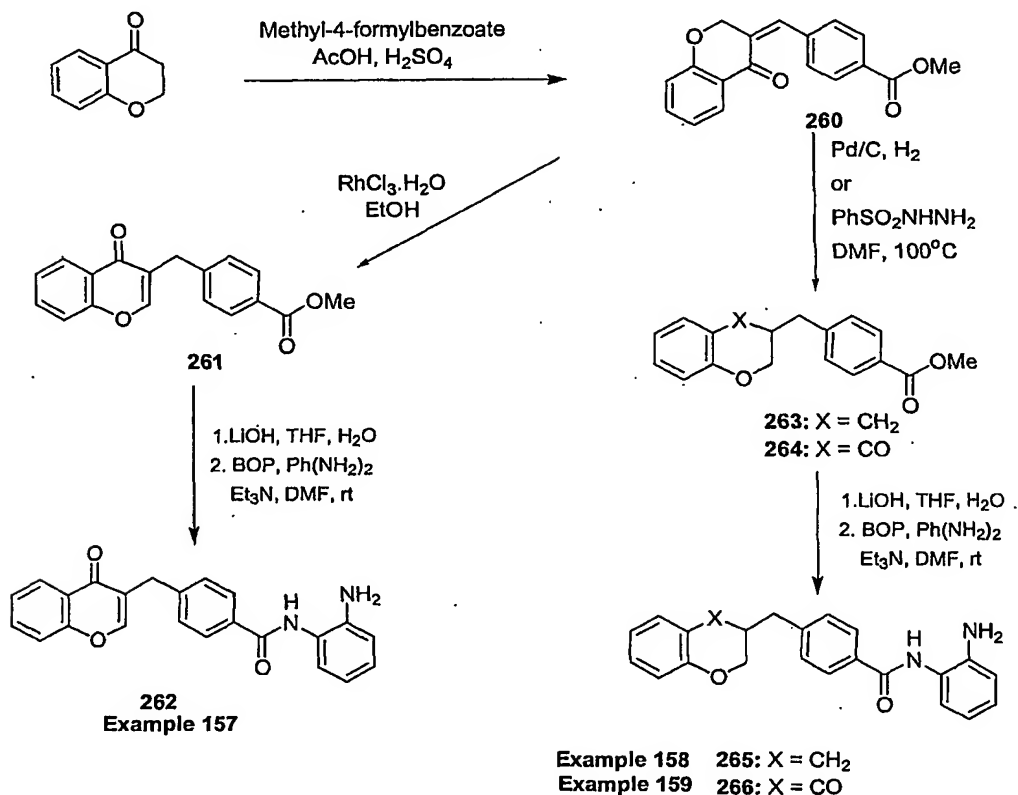
Step 1: Methyl 2-amino-4,5-dimethyl-thiophene-3-carboxylate (258)

[0321] The procedure described by Hozien (Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab and S. A. Ahmed; *Synht. Commun.* 1996, 26(20), 3733-3755.) was followed to afford the title compound 258 (1.44 g, 17%) as a yellow solid. LRMS: 197.1 (Calc.); 200.1 (found).

Steps 2: N-(2-Amino-phenyl)-4-(5,6-dimethyl-4-oxo-4H-thieno[2,3-d]pyrimidin-3-ylmethyl)-benzamide (259)

[0322] Following the procedure described in Example 155, step 1, 2 but substituting 258 for 256, the title compound 259 was obtained as a white solid (55%). ¹H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 8.57 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.16 (d, J = 7.7 Hz, 1H), 6.96 (dd, J = 7.6, 7.6 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.59 (dd, J = 7.4, 7.4 Hz, 1H), 5.25 (s, 2H), 4.87 (bs, 2H), 2.39 (s, 3H), 2.37 (s, 3H). LRMS: 404.1 (calc); 405.0 (found).

Scheme 46



Example 157

Step 1: Methyl 4-(4-oxo-chroman-3-ylidenemethyl)-benzoate (260)

[0323] Concentrated H₂SO₄ (2 ml) was slowly added to a solution of 4-chromanone (2.00 g, 13.50 mmol) and methyl-4-formylbenzoate (2.11 g, 12.86 mmol) in glacial acetic acid. The reaction mixture was stirred 16 h at room temperature. The solvent was concentrated to half volume the resulting precipitate was filtered and rinsed with ethyl acetate to afford the title compound 260 (3.11 g, 82%) as a purple solid. ¹H NMR: (DMSO) δ (ppm): 8.05 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 7.6 Hz, 1H), 7.79 (s, 1H), 7.64-7.59(m, 3H), 7.15 (dd, J = 7.6, 7.6 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 5.43 (s, 2H), 3.89 (s, 3H).

Step 2: Methyl-4-(4-oxo-4H-chromen-3-ylmethyl)-benzoate (261)

[0324] Water (0.2 ml) and RhCl₃·H₂O (7 mg, 0.034 mmol) was added to a suspension of compound 260 (200 mg, 0.680 mmol) in EtOH (2 ml) and CHCl₃ (2 ml). The reaction mixture was stirred 16 h at 70°C. The reaction mixture was cooled down and diluted in ethyl acetate, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (0.5-1% MeOH/CH₂Cl₂) to afford the title compound 261 (118 mg, 59%) as a white solid. ¹H NMR: (DMSO) δ (ppm): 8.45 (s, 1H), 8.03 (dd, J = 7.9, 1.8 Hz, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.83-7.77(m, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.50-7.43 (m, 3H), 3.82 (s, 3H), 3.80 (s, 2H).

Step 3: N-(2-Amino-phenyl)-4-(4-oxo-4H-chromen-3-ylmethyl)-benzamide (262)

[0325] The title compound 262 was obtained following the same procedure as Example 1, step 4, 5. ¹H NMR: (DMSO) δ (ppm): 9.56 (bs, 1H), 8.45 (s, 1H), 8.04 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.80 (dd, J = 7.5, 7.5 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.51-7.42 (m, 3H), 7.14 (d, J = 7.9 Hz, 1H), 6.96 (dd, J = 7.3, 7.3 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 6.58 (dd, J = 7.3, 7.3 Hz, 1H), 4.86 (bs, 2H), 3.80 (s, 2H). LRMS: 370.1 (calc.); 371.1 (found).

Example 158

Step 2: Methyl 4-chroman-3-ylmethyl-benzoate (263)

[0326] Pd/C 10% was added to a suspension of 260 (200 mg, 0.68 mmol) in MeOH (40 ml) and DMA (10 ml) which was previously purged

under vacuum. The reaction mixture was stirred during 4 h at room temperature. After evaporation of the MeOH, water was added to the oily residue and the precipitate obtained was filtered. The crude residue was then purified by flash chromatography on silica gel (5-8% AcOEt/Hex) to afford the title compound 263 (114 mg, 59%) as a white solid. LRMS: 282.1 (Calc.); 283.0 (found).

Step 3: N-(2-Amino-phenyl)-4-chroman-3-ylmethyl-benzamide (265)

[0327] The title compound 265 was obtained following the same procedure as Example 1, steps 4 and 5. ¹H NMR: (acetone) δ (ppm): 9.06 (bs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.08-6.98 (m, 3H), 6.87 (d, J = 7.5 Hz, 1H), 6.82-6.66 (m, 3H), 4.62 (s, 2H), 4.22-4.17 (m, 1H), 4.88-3.81 (m, 1H), 2.88-2.71 (m, 3H), 2.61-2.53 (m, 1H), 2.41-2.33 (m, 1H). LRMS: 358.2 (calc.); 359.1 (found).

Example 159

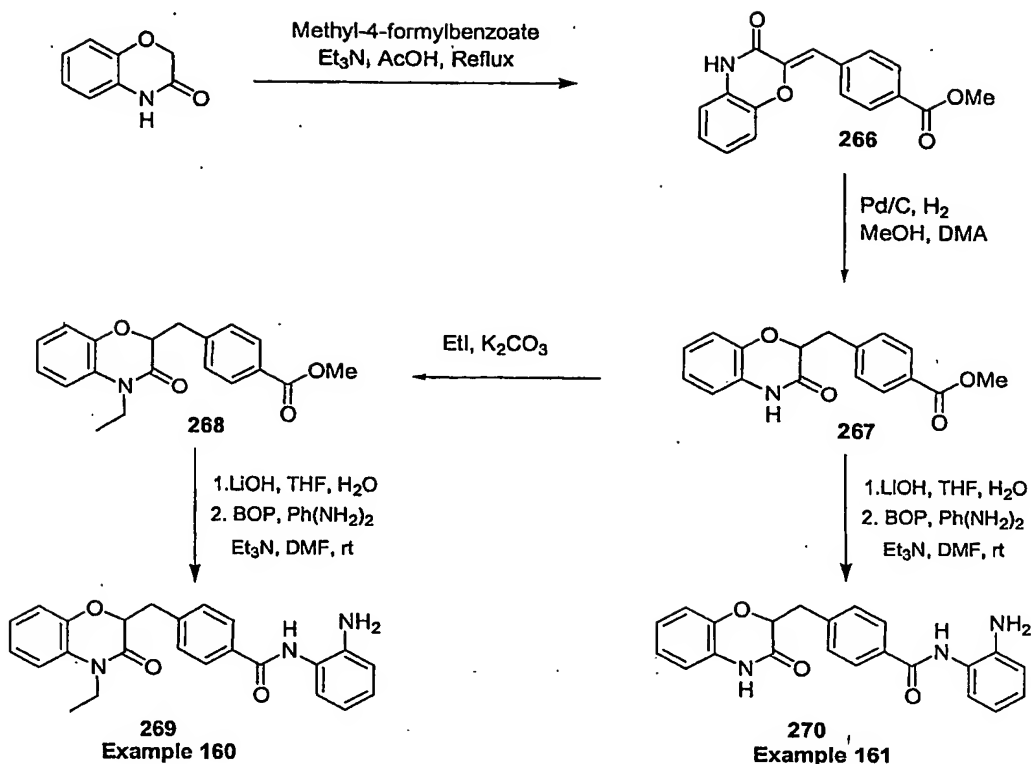
Step 2: Methyl 4-(4-oxo-chroman-3-ylmethyl)-benzoate (264)

[0328] A suspension of 260 (400 mg, 1.36 mmol) and benzenesulfonyl hydrazine (702 mg, 4.08 mmol) in DMF (7 ml) was stirred at 100°C during 48h. The solvent was evaporated and the residue was diluted in AcOEt, washed with NH₄Cl sat., brine, dried over anhydrous MgSO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5% AcOEt/HEX) to afford the title compound 264 (170 mg, 42%) as a white solid. LRMS: 296.1 (Calc.); 297.0 (found).

Step 3: N-(2-Amino-phenyl)-4-(4-oxo-chroman-3-ylmethyl)-benzamide (266)

[0329] The title compound 266 was obtained following the same procedure as Example 1, steps 4 and 5. ¹H NMR: (acetone) δ (ppm): 9.62 (bs, 1H), 7.93 (d, J = 7.9 Hz, 2H), 7.79 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 7.0, 7.0 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.17-7.04 (m, 3H), 6.97 (dd, J = 7.0, 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (dd, J = 7.5, 7.5 Hz, 1H), 4.88 (s, 2H), 4.44-4.39 (m, 1H), 4.28-4.21 (m, 1H), 2.26-3.21 (m, 2H), 2.83-2.74 (m, 1H). LRMS: 372.1 (calc.); 372.1 (found).

Scheme 47



Example 160

Step 1: Methyl 4-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzoate (266)

[0330] Et_3N (3.18 ml, 22.8 mmol) was added to a stirring solution of 2-H-1,4-benzoxazin-3-(4H)-one (2.50 g, 16.8 mmol) and methyl 4-formylbenzoate (4.59 g, 27.5 mmol) in Ac_2O (20 ml). The reaction mixture was refluxed 16h. After this mixture was cooled for 3 days, the solid was filtered and rinsed with ethyl acetate to afford the title compound 266 (657 mg, 13%) as a yellow solid. LRMS: 295.1 (Calc.); 296.0 (found).

Step 2: Methyl 4-(3-oxo-3,4-dihydro-benzo[1,4]oxazin-2-ylidenemethyl)-benzoate (267)

[0331] The title compound 267 was obtained following the same procedure as Example 158, step 2. LRMS: 297.1 (Calc.); 298.1 (found).

Step 3: N-(2-Amino-phenyl)-4-(4-ethyl-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-2-ylmethyl)-benzamide (269)

[0332] The title compound 269 was obtained from 267 following the same procedure as Example 99, step 2, 3, then followed by Example 1,

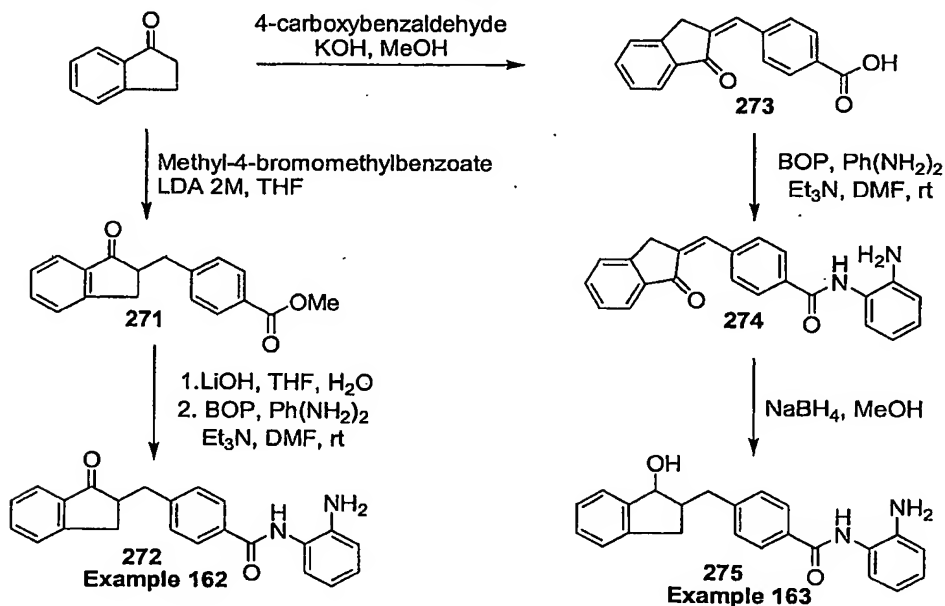
step 4, 5. ^1H NMR: (DMSO) δ (ppm): 9.61 (bs, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.11-6.91 (m, 4H), 6.77 (d, J = 7.0 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.95-4.91 (m, 1H), 4.89 (bs, 2H), 3.95 (q, J = 7.0 Hz, 2H), 3.28-3.22 (m, 1H), 3.17-2.89 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H). LRMS: 401.2 (calc.); 402.1 (obt.).

Example 161

Step 1: *N*-(2-Amino-phenyl)-4-(3-oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-2-ylmethyl)-benzamide (270)

[0333] The title compound 270 was obtained from 267 following the same procedure as Example 1, step 4, 5. ^1H NMR: (DMSO) δ (ppm): 10.74 (bs, 1H), 9.61 (bs, 1H), 7.91 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.99-6.85 (m, 5H), 6.78 (d, J = 7.5 Hz, 1H), 6.60 (dd, J = 7.0, 7.0 Hz, 1H), 4.92-4.89 (m, 3H), 3.29-3.23 (m, 1H), 3.15-3.07 (m, 1H). MS: (calc.) 373.1; (obt.) 374.1 (MH) $^+$.

Scheme 48



Example 162

Step 1: Methyl 4-(1-oxo-indan-2-ylmethyl)-benzoate (271)

[0334] A 2M LDA solution in THF (4.16 ml, 8.32 mmol) was added to a solution of indanone (1.00 g, 7.57 mmol) in THF (10 ml) at -60°C . The solution was slowly warmed to 0°C during a period of 15 min. and was

agitated for 15 more min. The reaction was then cooled to -78°C and a solution of methyl-4-bromobenzoate (1.73 g, 7.57 mmol) was slowly added. The solution was slowly warmed to -20°C and stirred during 4 hours. The reaction mixture was quenched with HCL 1M and the solvent was evaporated. The residue was diluted in ethyl acetate, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (5-20% AcOEt/HEX) to afford the title compound 271 (245 mg, 17%) as a white solid. LRMS: 280.1 (Calc.); 281.1 (found).

Step 2: N-(2-Amino-phenyl)-4-(1-oxo-indan-2-ylmethyl)-benzamide (272)

[0335] The title compound 272 was obtained following the same procedure as Example 1, step 4, 5. ^1H NMR: (DMSO) δ (ppm): 9.59 (bs, 1H), 7.91 (d, $J = 7.6$ Hz, 2H), 7.69-7.64 (m, 2H), 7.54 (d, $J = 7.6$ Hz, 1H), 7.45-7.40 (m, 3H), 7.16 (d, $J = 8.2$ Hz, 1H), 6.96 (dd, $J = 7.3, 7.3$ Hz, 1H), 6.77 (d, $J = 8.2$ Hz, 1H), 6.59 (dd, $J = 7.3, 7.3$ Hz, 1H), 4.87 (bs, 2H), 3.23-3.14 (m, 3H), 2.85-2.81 (m, 2H). LRMS: 356.1 (calc.); 357.2 (found).

Example 163

Step 1: 4-(1-Oxo-indan-2-ylidenemethyl)-benzoic acid (273)

[0336] To a suspension of indanone (2.00 g, 15.1 mmol) and 4-carboxybenzaldehyde (1.89g, 12.6 mmol) in EtOH (10 ml) was added KOH (1.77 g, 31.5 mmol) at 0°C . The reaction mixture was stirred 30 min at 0°C then at room temperature for 16 h. The solvent was evaporated and the residue was dissolved in water, acidified to pH 5 with HCL 1 M. The precipitate was filtered and rinsed with water to afford the title compound 273 (2.27 g, 57%) as a yellow solid. LRMS: 264.1 (Calc.); 265.0 (found).

Step 2: N-(2-Amino-phenyl)-4-(1-oxo-indan-2-ylidenemethyl)-benzamide (274)

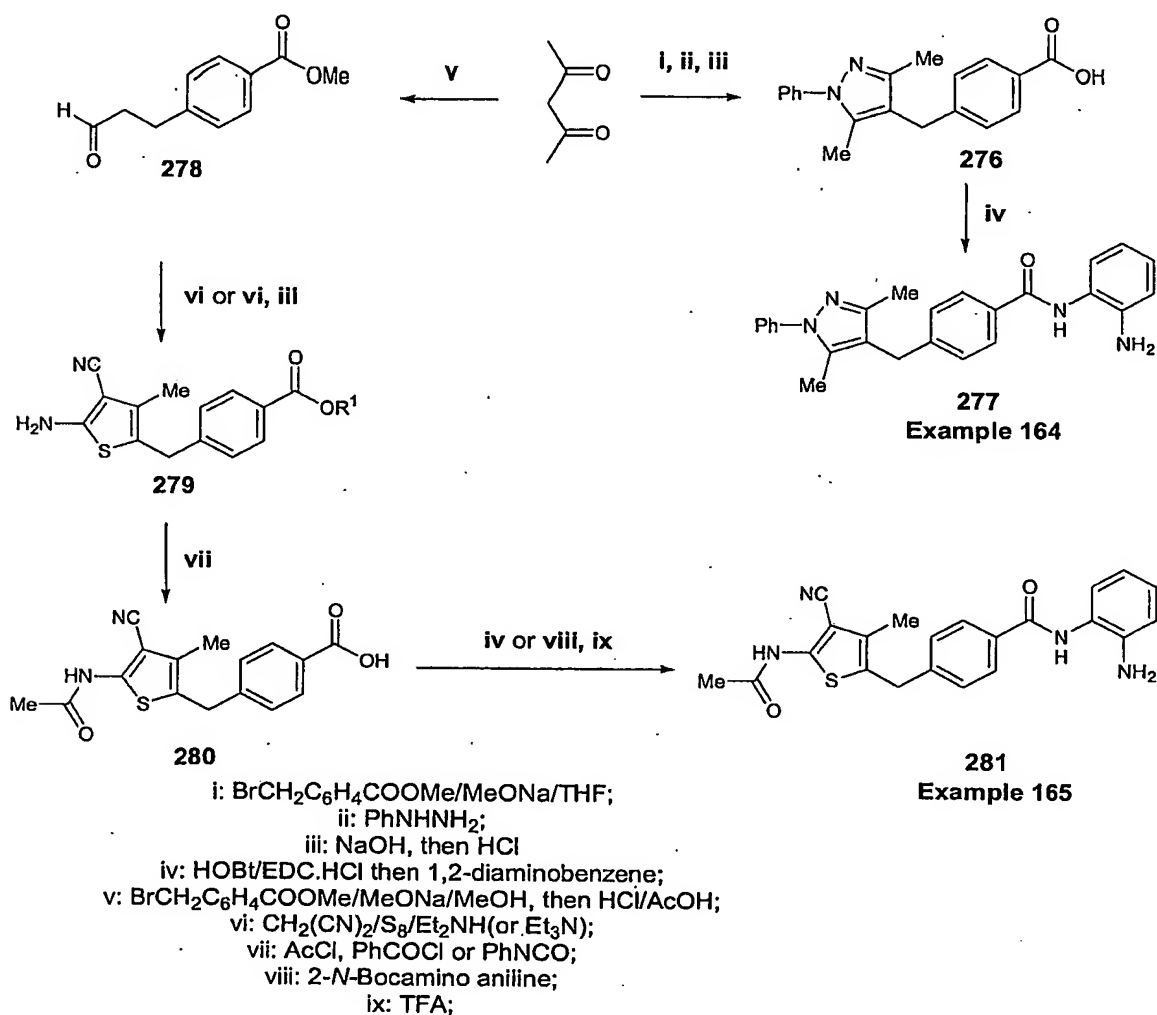
[0337] The title compound 274 was obtained following the same procedure as Example 1, step 5. LRMS: 354.1 (Calc.); 355.0 (found).

Step 3: N-(2-Amino-phenyl)-4-(1-hydroxy-indan-2-ylmethyl)-benzamide (275)

[0338] To a suspension of 274 (300 mg, 0.85 mmol) in MeOH (8 ml) and water (1 ml) was added NaBH_4 (75 mg, 1.95 mmol). The reaction mixture was stirred at 50°C 16h and cooled down. Water was added to

the solution and the precipitated was filtered and rinsed with cold water to afford the title compound 275 (224 mg, 74%) as a white solid. ^1H NMR: (acetone) δ (ppm): 9.05 (bs, 1H), 8.00 (dd, $J = 8.2$, 2.7 Hz, 2H), 7.47 (d, $J = 8.5$ Hz, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.38-7.30 (m, 2H), 7.22-7.12 (m, 3H), 7.01 (ddd, $J = 7.6$, 7.6, 1.5 Hz, 1H), 6.87 (dd, $J = 8.0$, 1.1 Hz, 1H), 6.68 (dd, $J = 7.6$, 7.6 Hz, 1H), 4.98 (t, $J = 5.8$ Hz, 0.4H), 4.89 (t, $J = 6.7$ Hz, 0.6H), 4.63 (bs, 2H), 4.45 (d, $J = 6.9$ Hz, 0.6H), 4.06 (d, $J = 6.0$ Hz, 0.4H), 3.30-3.19 (m, 1H), 2.88-2.48 (m, 3H, CH_2). LRMS: 358.2 (calc.); 359.1 (found).

Scheme 49



Example 164**Step 1: 4-(3,5-Dimethyl-1-phenyl-1H-pyrazol-4-ylmethyl)-benzoic acid (276)**

[0339] To a solution of NaH (60% in mineral oil, 250 mg, 6.3 mmol) at 0°C. acetyl acetone (0.646 ml, 6.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester 2 (1.2 g, 5.2 mmol). The reaction mixture stirred 1 hour at room temperature and refluxed for 2 hours. Phenyl hydrazine (0.51 ml, 5.2 mmol) was added and the reaction mixture refluxed for an additional hour. THF was removed in vacuum and the oily residue was partitioned between water and ethyl acetate. Organic layer was separated, dried, evaporated and purified by chromatography on a silica gel column, eluent EtOAc - hexane (1:1) to produce an oily material (800mg) which was treated with a solution of NaOH (0.8 g, 20 mmol) in 20 ml water for 1 hour at room temperature. The following steps, - acidification with HCl (pH 6), extraction of the resultant emulsion with ethyl acetate, drying the extract with sodium sulfate, evaporation and column chromatography (eluent EtOAc - hexane, 1:1) afforded 390 mg of a mixture of 276 (the title compound) and 278 (molar ratio 1:2). $[M-1]^+$ 307.0 and 191.1. This mixture was taken for the next step as is.

Step 2. N-(2-Amino-phenyl)-4-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-ylmethyl)-benzamide (277)

[0340] Following a procedure analogous to that described in Example 92, step 2, but substituting 276 for 143, the title compound 277 was obtained in 25% yield (purified by chromatography using as eluent EtOAc - hexane, 1:1). ^1H NMR: (300 MHz, DMSO- d_6 , δ (ppm): 9.64 (s, 1H); 7.97 (d, J = 7.6 Hz, 2H), 7.42-7.56 (m, 5H), 7.37 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 4.93 (s, 2H), 3.92 (s, 2H), 2.34 (s, 3H), 2.18 (s, 3H).

Example 165**Step 1: 4-(3-Oxo-butyl)-benzoic acid (278)**

[0341] To a solution of acetyl acetone (5.0 ml, 49 mmol) at room temperature NaOMe (25% wt, 10.8 ml, 47.3 mmol) was added followed by 4-bromomethyl-benzoic acid methyl ester 2 (9.0 g, 39.3 mmol). The reaction mixture refluxed 3 hours, cooled to the room temperature and acidified with HCl (pH 1-2). Evaporation of the resultant

solution yielded a residue, which was refluxed in a mixture of glacial AcOH (50 ml) and conc. HCl (25 ml) for 4 hours. Acids were removed in vacuum and the residue was triturated with water to form a crystalline material, which was collected by filtration and dried to afford **278** (6.72 g, 80% yield). [M-1] 191.1.

Step 2. 4-(5-Amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 279

[0342] To a refluxing suspension of 4-(3-oxo-butyl)-benzoic acid **278** (700 mg, 3.65 mmol), malonodinitrile (241 mg, 3.65 mmol) and sulfur (130 mg, 3.65 mmol) in 20 ml EtOH, diethylamine (0.5 ml, 4.8 mmol) was added. The reaction mixture refluxed 1 hour, cooled to the room temperature, acidified with conc. HCl (pH 4-5) and evaporated to yield a solid residue. This material was partitioned between water and ethyl acetate, organic layer was separated, dried, evaporated and chromatographed on a silica gel column, eluent EtOAc-hexane, 1:1, to afford the title compound **279** (300 mg, 30% yield). ¹H NMR: (300 MHz, DMSO-d₆, δ ppm): 7.87 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 6.98 (s, 2H), 3.92 (s, 2H), 2.03 (s, 3H).

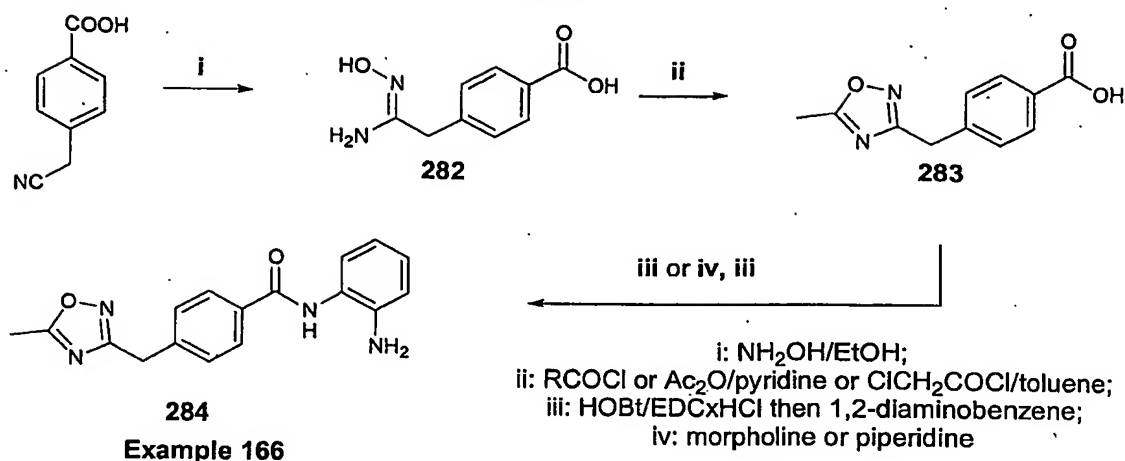
Step 3. 4-(5-Acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid 280

[0343] To a solution of 4-(5-amino-4-cyano-3-methyl-thiophen-2-ylmethyl)-benzoic acid **279** (230 mg, 0.86 mmol) in a solvent mixture acetone (5 ml) - dichloromethane (5 ml) at room temperature acetyl chloride (0.305 ml, 4.3 mmol) was added. After 2 hours of stirring at the same conditions a precipitate of the title compound **280** formed which was collected and dried (200 mg, 75% yield). [M-1] 313.1.

Step 4: N-(2-Amino-phenyl)-4-(5-acetylamino-4-cyano-3-methyl-thiophen-2-ylmethyl)- benzamide (281)

[0344] Following a procedure analogous to that described in Example 92, step 2, but substituting **280** for **143**, the title compound **281** was obtained in 25% yield. ¹H NMR (DMSO) δ (ppm): 9.61 (s, 1H); 7.91 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 6.6 Hz, 1H), 6.77 (d, J = 7.0 Hz, 1H), 6.59 (t, J = 7.9 Hz, 1H), 4.89 (s, 2H), 4.10 (s, 2H), 2.19 (s, 3H), 2.16 (s, 3H). [M+1] 405.0.

Scheme 50



Example 166

Step 1. 4-(N-Hydroxycarbamimidoylmethyl)-benzoic acid (282)

[0345] A suspension of 4-cyanomethyl benzoic acid (2.07 g, 12.86 mmol), $\text{NH}_2\text{OH} \cdot \text{HCl}$ (1.79 g, 25.71 mmol) and potassium hydroxide (2.16 g, 38.57 mmol) in 70 ml ethanol refluxed for 36 hours, poured into 100 ml water and acidified with conc. HCl (pH 5-6). EtOH was removed in vacuum and the remaining suspension was treated with another 100 ml water. A precipitate formed which was collected and dried to afford the title compound 282. $[\text{M}+1]^+ 195.1$.

Step 2. 4-(5-Methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzoic acid (283)

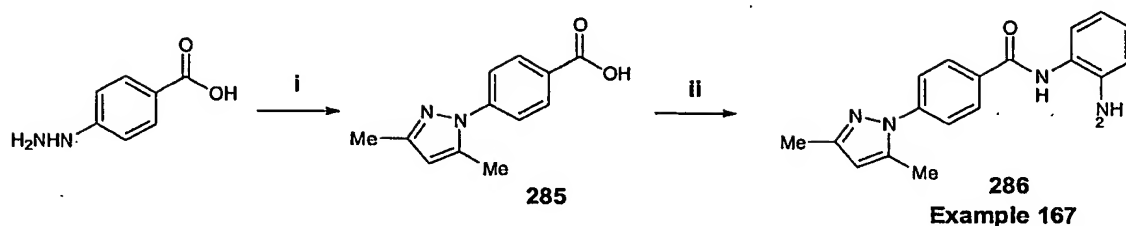
[0346] A solution of 4-(N-hydroxycarbamimidoylmethyl)-benzoic acid 282 (388 mg, 2.0 mmol) in pyridine (8 ml) was treated with acetic anhydride (0.283 ml, 3.0 mmol). The resultant solution refluxed 6 hours, evaporated in vacuum and the remaining solid was triturated with water, collected by filtration, dried and purified by chromatography on a silica gel column, eluent EtOAc, EtOAc-MeOH (10:1) and finally EtOAc-MeOH (1:1), to produce 283 (164 mg, 38% yield). $[\text{M}-1]^- 217.1$

Step 3. N-(2-Amino-phenyl)-4-(5-methyl-[1,2,4]oxadiazol-3-ylmethyl)-benzamide (284)

[0347] For the preparation of the title compound 284, a procedure analogous to that described in Example 92, step 2, but substituting 283 for 143, the title compound 284 was obtained. ^1H NMR: (DMSO) δ (ppm): 9.62 (s, 1H), 7.93 (d, $J = 7.9$ Hz, 2H), 7.42 (d, $J = 8.4$ Hz, 1H), 7.16 (d, $J = 7.5$ Hz, 1H), 6.97 (t, $J = 7.9$ Hz, 1H), 6.78 (d, J

= 7.5 Hz, 1H), 6.60 (t, J = 7.9 Hz, 1H), 4.92 (s, 2H), 4.14 (s, 2H), 2.55 (s, 3H). [M+1]⁺ 309.2

Scheme 51



i: Acetyl acetone/EtOH;
ii: HOBt/EDC·HCl then 1,2-diaminobenzene;

Example 167

Step 1: 4-(3,5-Dimethyl-pyrazol-1-yl)-benzoic acid (285)

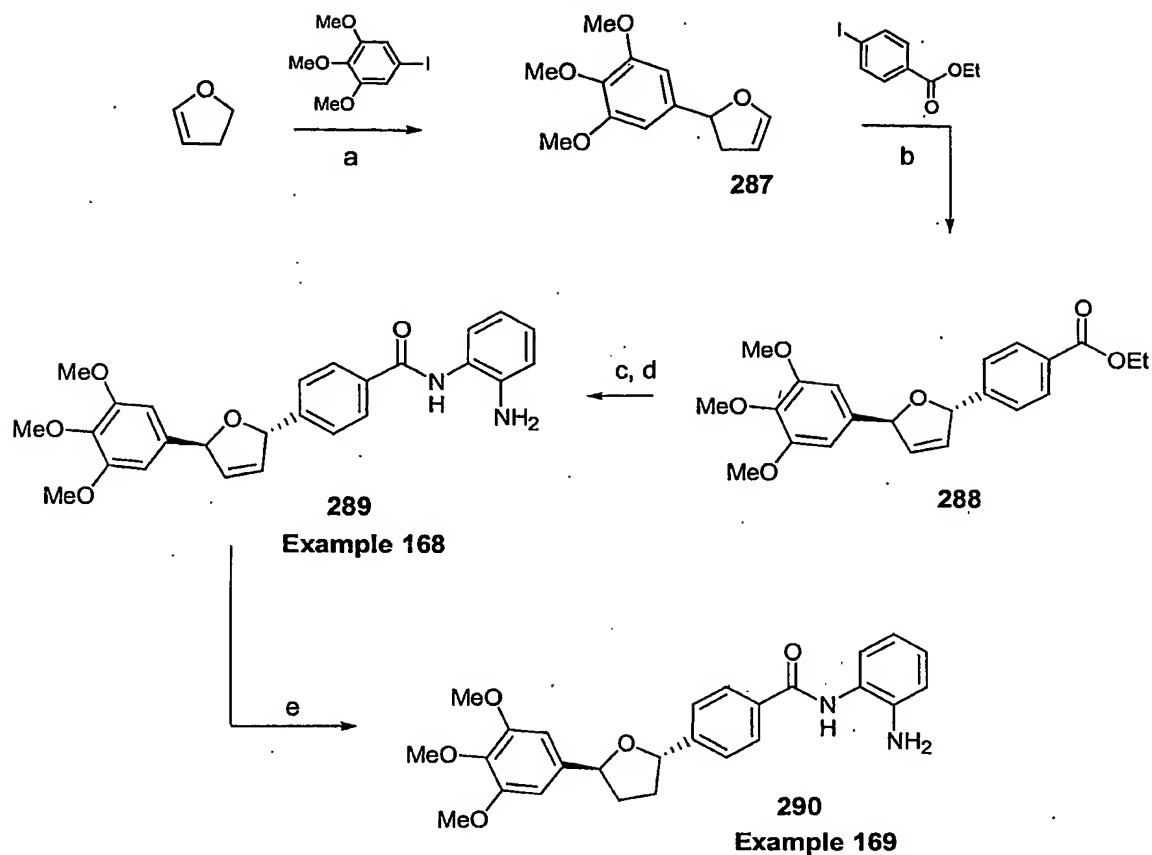
[0348] A solution of 4-hydrazino-benzoic acid (0.60 g, 3.95 mmol) and acetyl acetone (0.405 ml, 3.95 mmol) in ethanol (20 ml) refluxed for 1 hour. Ethanol was removed in vacuum and the remaining solid was triturated with water and collected by filtration to produce 285 (0.71 mg, 83% yield). [M-1]⁻ 215.1.

Step 2: N-(2-Amino-phenyl)-4-(3,5-dimethyl-pyrazol-1-yl)-benzamide (286)

[0349] For the preparation of the title compound 286, a procedure analogous to that described in Example 92, step 2, but substituting 285 for 143, the title compound 286 was obtained in 34% yield (purified by chromatography using as eluent CH₂Cl₂-methanol, 19:1).

¹H NMR: (DMSO) δ (ppm): 9.73 (s, 1H); 8.09 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 6.98 (t, J = 7.0 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 6.13 (s, 1H), 4.92 (s, 2H), 2.37 (s, 3H), 2.20 (s, 3H). [M+1]⁺ 303.3

Scheme 52



- a. 2.5% Pd(OAc)₂ / nBu₄NCl (1 eq) / KOAc (3 eq) / 2.5% PPh₃ / DMF / 80°C
 b. 3-4% Pd(OAc)₂ / 9% PPh₃ / Ag₂CO₃ (2 eq) / CH₃CN / 80°C
 c. LiOH · H₂O / THF-H₂O (2:1)
 d. 1,2-phenylenediamine / BOP / Et₃N / DMF
 e. PtO₂ / H₂ (1 atm) / AcOEt

Example 168

Step 1: 2-(3,4,5-Trimethoxy-phenyl)-2,3-dihydro-furan (287)

[0350] To a solution of 5-iodo-1,2,3-trimethoxybenzene (900 mg, 3.06 mmol) and 2,3-dihydrofuran (1.16 mL, 15.3 mmol) in dry DMF (8 mL) were added PPh₃ (20 mg, 0.077 mmol), KOAc (901 mg, 9.18 mmol), n-Bu₄NCl (850 mg, 3.06 mmol) and Pd(OAc)₂ (17 mg, 0.077 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was diluted with AcOEt and water. After separation, the organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 20/80) to afford the title compound 287 (311 mg, 1.32 mmol, 43% yield). ¹H NMR: (300 MHz, CDCl₃) δ (ppm): 6.59 (s, 2H), 6.45 (m, 1H), 5.45 (dd, J = 10.5, 8.4

Hz, 1H), 4.97 (m, 1H), 3.87 (s, 6H), 3.84 (s, 3H), 3.06 (m, 1H), 2.62 (m, 1H).

Step 2: 4-[5-(3,4,5-Trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzoic acid ethyl ester (288)

[0351] To a solution of 287 (200 mg, 0.846 mmol) and 4-Iodo-benzoic acid ethyl ester (468 mg, 1.69 mmol) in dry acetonitrile (4 mL) were added PPh₃ (20 mg, 0.076 mmol), Ag₂CO₃ (467 mg, 1.69 mmol) and Pd(OAc)₂ (7 mg, 0.03 mmol). The reaction mixture was stirred 18 h at 80°C. The reaction mixture was filtered through celite and washed with AcOEt. Water was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 30/70) to afford the title compound 288 (280 mg, 0.728 mmol, 86% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.05 (d, J = 7.5 Hz, 2H), 7.45 (d, J = 7.5 Hz, 2H), 6.61 (s, 2H), 6.18-5.95 (m, 4H), 4.38 (q, J = 7.0 Hz, 2H), 3.88 (s, 6H), 3.84 (s, 3H), 1.39 (t, J = 7.0 Hz).

Step 3: N-(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-2,5-dihydro-furan-2-yl]-benzamide (289)

[0352] Following a procedure analogous to that described in Example 1, step 4, 5, but substituting 288 for 6, the title compound 289 was obtained in 48% yield. ¹H NMR (DMSO) δ (ppm): 8.00 (s, 1H), 7.91 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.92-6.82 (m, 2H), 6.61 (s, 2H), 6.14-5.99 (m, 4H), 3.89 (s, 6H), 3.84 (s, 3H).

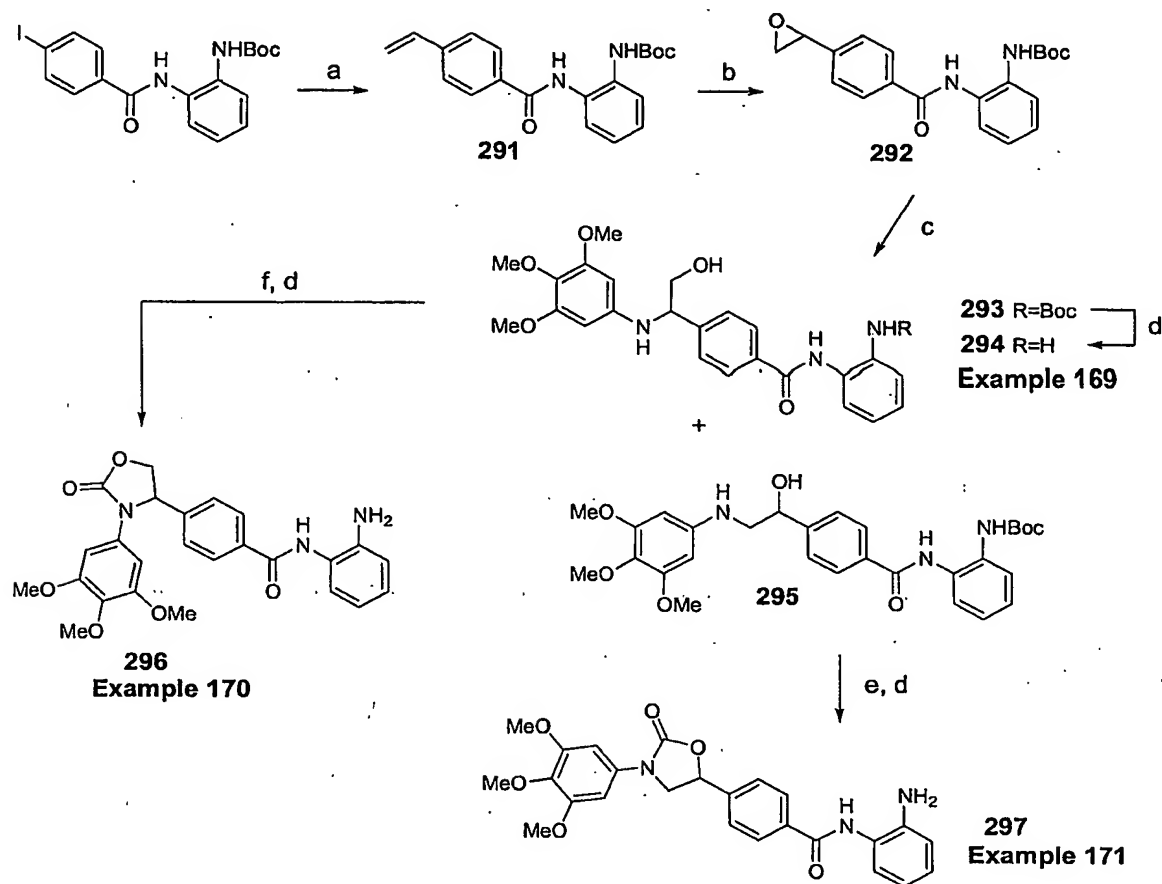
Example 169

Step 1: N-(2-Amino-phenyl)-4-[5-(3,4,5-trimethoxy-phenyl)-tetrahydro-furan-2-yl]-benzamide. (290)

[0353] To a degazed solution of 289 (43 mg, 0.096 mmol) in AcOEt (4 mL) was added PtO₂ (3 mg, 0.01 mmol) and the reaction mixture was stirred at room temperature under a 1 atm pressure of H₂ for 16 h. The reaction flask was purged with N₂ then the reaction mixture was filtered through celite, rinsed with MeOH and concentrated. The crude residue was purified three times by flash chromatography on silica gel (MeOH/DCM: 2/98, AcOEt/DCM: 30/70 and AcOEt/CHCl₃: 30/70) to afford the title compound 290 (10 mg, 0.22 mmol, 23% yield). ¹H NMR (CDCl₃) δ (ppm): 8.10 (s, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H),

6.96-6.85 (m, 2H), 6.64 (s, 2H), 5.33 (t, $J = 7.0$ Hz, 1H), 5.21 (t, $J = 7.0$ Hz, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 2.59-2.40 (m, 2H), 2.09-1.88 (m, 2H).

Scheme 53



- a. Tributyl(vinyl)tin / $\text{Pd}(\text{PPh}_3)_4$ / Toluene / 100°C
- b. *m*-CPBA / CHCl_3 / r.t.
- c. 3,4,5-trimethoxyaniline / CoCl_2 / CH_3CN
- d. TFA / DCM
- e. 1,1'-carbonyldiimidazole / DCM / r.t.
- f. 1,1'-carbonyldiimidazole / Et_3N / Toluene / THF / 90°C

Example 169

Step 1: [2-(4-Vinyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (291)

[0354] Following a procedure analogous to that described in Example 143, step 2, but substituting 184 for 221, the title compound 291

was obtained in 90% yield as a dark yellow oil. ^1H NMR: (300 MHz, CDCl_3) δ (ppm): 9.18 (s, 1H), 7.94 (d, $J = 8.5$ Hz, 2H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.49 (d, $J = 8.5$ Hz, 2H), 7.30-7.10 (m, 3H), 6.89 (s, 1H), 6.77 (dd, $J = 17.4, 11.0$ Hz, 1H), 5.87 (d, $J = 17.4$ Hz, 1H), 5.39 (d, $J = 11.0$ Hz, 1H), 1.52 (s, 9H).

Step 2: [2-(4-Oxiranyl-benzoylamino)-phenyl]-carbamic acid tert-butyl ester (292)

[0355] To a solution of 291 (4.1 g, 12.1 mmol) in dry CHCl_3 (60 mL) was added *m*-CPBA 70% (3.6 g, 14.5 mmol). The reaction mixture was stirred at room temperature for 5 h then additional *m*-CPBA (0.6 g, 2.4 mmol) was added and the stirring continued for 1 h. A further amount of *m*-CPBA (0.6 g, 2.4 mmol) was added and the reaction mixture was stirred for 16 h. Chloroform and a 10% solution of NaHCO_3 were added and the phases were separated. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/Hexane: 1/3) to afford the title compound 292 (2.86 g, 8.07 mmol, 66% yield). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 9.20 (s, 1H), 7.95 (d, $J = 8.1$ Hz, 2H), 7.86-7.75 (m, 1H), 7.38 (d, $J = 8.1$ Hz, 2H), 7.26-7.10 (m, 3H), 6.84-6.70 (m, 1H), 3.93 (t, $J = 3.0$ Hz, 1H), 3.20 (t, $J = 5.0$ Hz, 1H), 2.80 (dd, $J = 5.0, 3.0$ Hz, 1H), 1.52 (s, 9H).

Step 3: (2-{4-[1-Hydroxy-2-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (295) and (2-{4-[2-Hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (293)

[0356] To a stirred solution of CoCl_2 (8 mg, 0.06 mmol) in dry acetonitrile (10 mL) was added 292 (1 g, 2.8 mmol) followed by 3,4,5-trimethoxyaniline (516 mg, 2.8 mmol) and the reaction mixture was allowed to react for 16 h at room temperature then it was heated at 60°C for 5 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (AcOEt/Hexane: 1/1) to afford compounds 293 and 295 (combined: 1.07 g, 1.99 mmol, 71% yield, ratio 292/295 = 5/1) which can be separated by flash chromatography on silica gel (AcOEt/Hexane: 1/1). ^1H NMR (300 MHz, CDCl_3) δ (ppm): Compound 292:

9.21 (s, 1H), 7.92 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 6.6 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.28-7.10 (m, 3H), 6.90 (s, 1H), 5.83 (s, 2H), 4.54-4.44 (m, 1H), 3.93 (dd, J = 8.1, 3.9 Hz, 1H), 3.84-3.72 (m, 1H), 3.71 (s, 3H), 3.66 (s, 6H), 1.47 (s, 9H). Compound 295: 9.22 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 8.1 Hz, 2H), 7.30-7.21 (m, 3H), 6.88 (s, 1H), 6.15 (s, 2H), 5.16-5.06 (m, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.50-3.25 (m, 2H), 1.51 (s, 9H).

Step 4: N-(2-Amino-phenyl)-4-[2-hydroxy-1-(3,4,5-trimethoxy-phenylamino)-ethyl]-benzamide (294)

[0357] Following a procedure analogous to that described in Example 42, step 3, but substituting 293 for 46, the title compound 294 was obtained in 50% yield. ¹H NMR (DMSO) δ (ppm): 8.36 (s, 1H), 7.74 (d, J = 6.9 Hz, 2H), 7.30 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 6.9 Hz, 1H), 7.00 (t, J = 7.2 Hz, 1H), 6.72 (m, 2H), 5.69 (s, 2H), 4.34 (m, 1H), 4.02-3.52 (m, 2H), 3.66 (s, 3H), 3.57 (s, 6H).

Example 170

Step 1: N-(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-4-yl]-benzamide (296)

[0358] To a solution of 293 (200 mg, 0.372 mmol) in toluene (5 mL) and THF (1 mL) was added 1,1'-carbonyldiimidazole (72 mg, 0.45 mmol) followed by Et₃N (156 μL, 1.12 mmol) and the mixture was stirred at room temperature for 5 h then at 90°C for 48 h. The reaction mixture was diluted with AcOEt, a solution of sat. NH₄Cl was added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (DCM/AcOEt: 80/20) to afford the desired compound (120 mg, 0.21 mmol, 57% yield). ¹H NMR (DMSO) δ (ppm): 9.37 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.76 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 7.25-7.15 (m, 3H), 6.88 (s, 1H), 6.61 (s, 2H), 5.40 (dd, J = 8.7, 6.0 Hz, 1H), 4.79 (t, J = 8.7 Hz, 1H), 4.19 (dd, J = 8.7, 6.0 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 6H), 1.47 (s, 9H).

[0359] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for 46, the title compound 296 was obtained in 81% yield. ¹H NMR (DMSO) δ (ppm): 8.03 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H),

7.30 (d, $J = 7.5$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 6.82 (d, $J = 7.5$ Hz, 2H), 6.61 (s, 2H), 5.40 (dd, $J = 8.7, 6.0$ Hz, 1H), 4.78 (t, $J = 8.7$ Hz, 1H), 4.18 (dd, $J = 8.7, 6.0$ Hz, 1H), 3.75 (s, 3H), 3.71 (s, 6H).

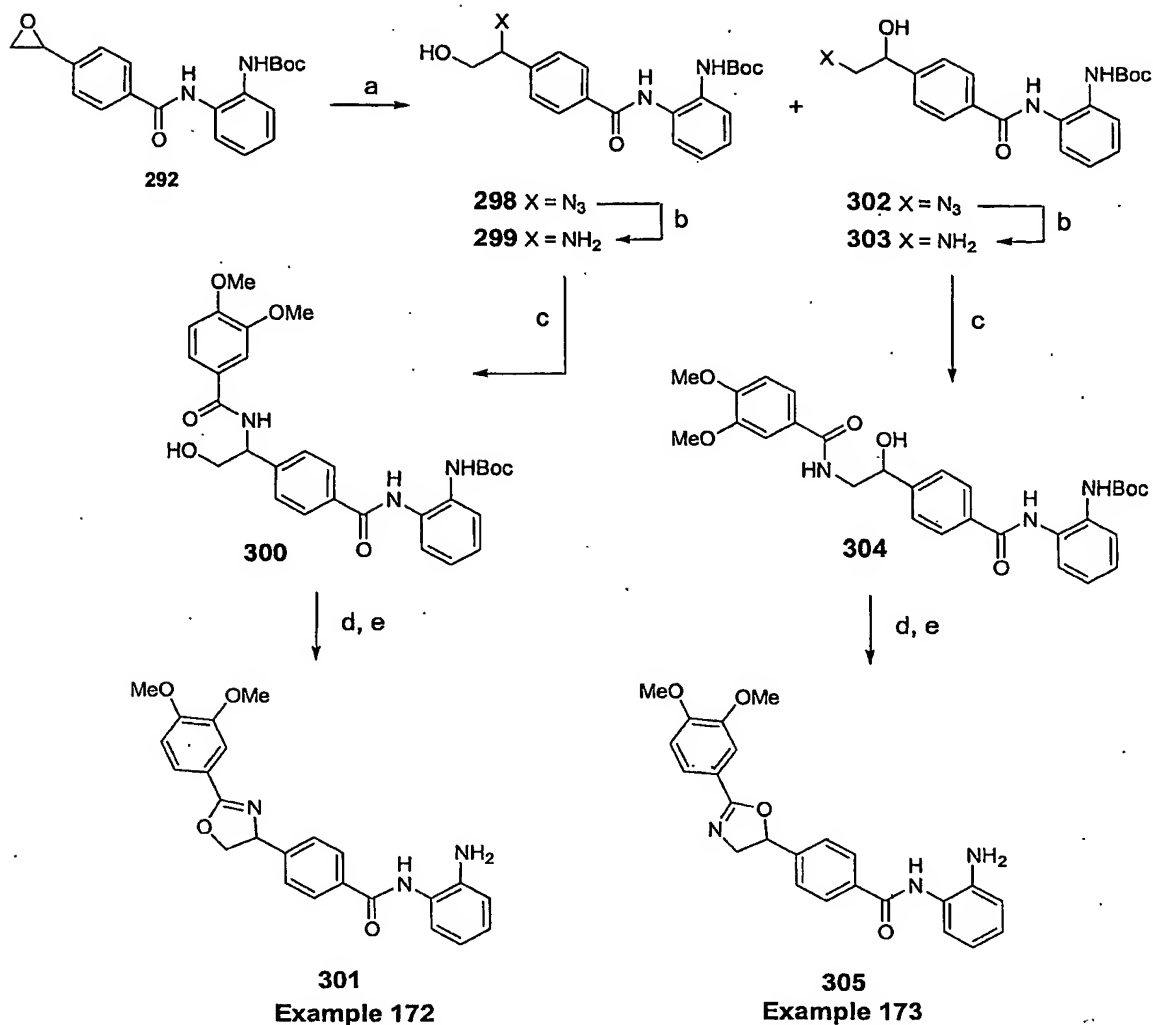
Example 171

Step 1: N-(2-Amino-phenyl)-4-[2-oxo-3-(3,4,5-trimethoxy-phenyl)-oxazolidin-5-yl]-benzamide (297)

[0360] To a solution of 295 (130 mg, 0.242 mmol) in DCM (2 mL) was added 1,1'-carbonyldiimidazole (47 mg, 0.29 mmol) and the mixture was stirred at room temperature for 16 h. DCM was removed under reduced pressure, AcOEt and a solution of sat. NH_4Cl were added and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (Hexane/AcOEt: 30/70) to afford the desired compound (80 mg, 0.14 mmol, 58% yield). ^1H NMR (DMSO) δ (ppm): 9.39 (s, 1H), 8.04 (d, $J = 8.1$ Hz, 2H), 7.84 (d, $J = 7.5$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 2H), 7.26-7.12 (m, 3H), 6.86-6.74 (m, 3H), 5.70 (t, $J = 8.4$ Hz, 1H), 4.24 (t, $J = 8.7$ Hz, 1H), 3.97-3.87 (m, 1H), 3.87 (s, 6H), 3.82 (s, 3H), 1.52 (s, 9H).

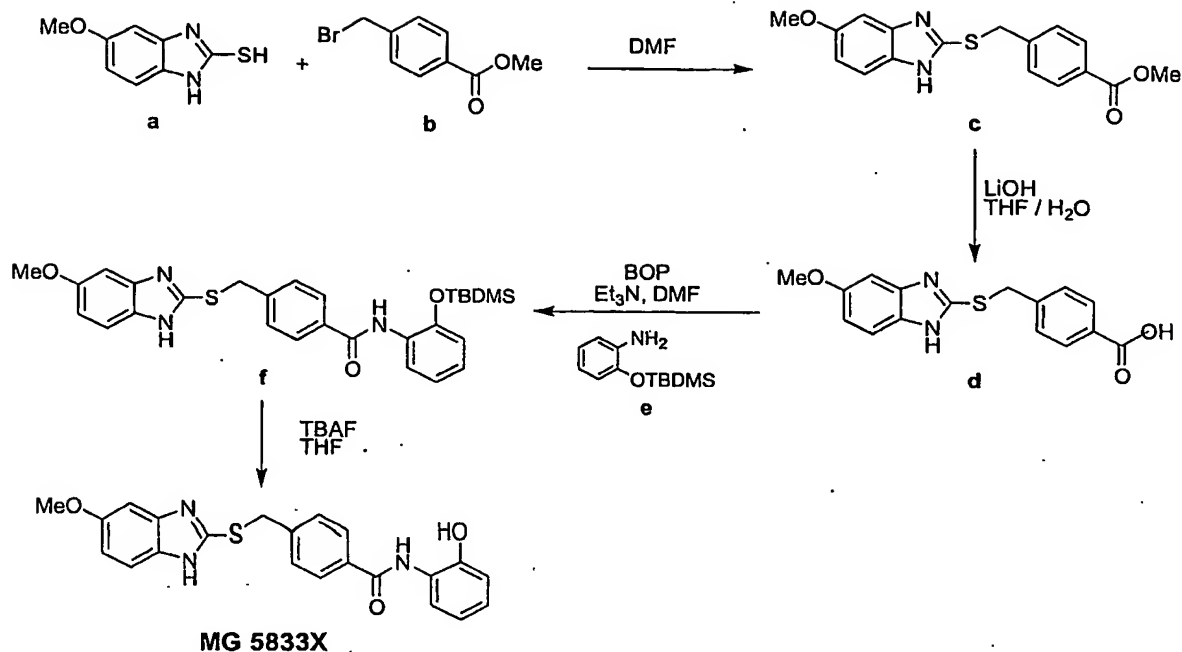
[0361] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for 46, the title compound 297 was obtained in 94% yield. ^1H NMR (DMSO) δ (ppm): 8.38 (s, 1H), 7.97 (d, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.35 (d, $J = 7.0$ Hz, 1H), 7.08 (t, $J = 7.0$ Hz, 1H), 6.97-6.87 (m, 2H), 6.79 (s, 2H), 5.66 (t, $J = 8.1$ Hz, 1H), 4.41 (t, $J = 9.0$ Hz, 1H), 3.91 (t, $J = 7.8$ Hz, 1H), 3.86 (s, 6H), 3.82 (s, 3H).

Scheme 54



a. CeCl_3 heptahydrate / NaN_3 / $\text{CH}_3\text{CN} - \text{H}_2\text{O}$ (9 : 1) / reflux
b. H_2 / Pd/C (10%) / MeOH
c. 3,4-dimethoxybenzoyl chloride / Et_3N / DCM / -20°C to r.t.
d. Burgess reagent / THF / 70°C
e. TFA / DCM

Scheme 55



Example 172

Step 1: {2-[4-(1-Azido-2-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (298) and {2-[4-(2-Azido-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (302)

[0362] To a solution of **292** (210 mg, 0.59 mmol) in acetonitrile (9 mL) and water (1 mL) was added CeCl_3 heptahydrate (110 mg, 0.296 mmol) followed by NaN_3 (42 mg, 0.65 mmol). The reaction mixture was refluxed for 3 h then acetonitrile was removed under reduced pressure. The residue was diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. Purification by flash chromatography on silica gel (AcOEt/Hexane: 1/1) afforded a 1:1 mixture of title compounds **298** and **302** (combined: 187 mg, 0.47 mmol, 80% yield) which were separated by flash chromatography on silica gel (AcOEt/Hexane: 2/5). Compound 298: ^1H NMR: (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ (ppm): 7.95 (d, $J = 8.1$ Hz, 2H), 7.70-7.63 (m, 1H), 7.43 (d, $J = 8.1$ Hz, 2H), 7.36-7.29 (m, 1H), 7.24-7.14 (m, 2H), 4.69 (dd, $J = 7.5, 4.8$ Hz, 1H), 3.80-3.65 (m, 2H), 1.49 (s, 9H). Compound 302: ^1H NMR: (300 MHz, CDCl_3) δ (ppm): 9.28 (s, 1H), 7.86 (d, $J = 8.4$ Hz, 2H), 7.71 (d, $J = 7.5$ Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 2H), 7.25-7.08 (m, 3H), 7.01 (s, 1H), 4.87 (dd, $J = 6.9, 5.1$ Hz, 1H), 3.47-3.38 (m, 2H), 3.32-3.21 (bs, 1H), 1.50 (s, 9H).

Step 2: {2-[4-(1-Amino-2-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (299)

[0363] To a solution of 298 (156 mg, 0.39 mmol) in MeOH (2 mL) was added Pd/C 10% (20 mg, 0.02 mmol). The reaction mixture was stirred under a 1 atm pressure of H₂ at room temperature for 16 h then it was purged with N₂. The palladium was removed by filtration through celite and the MeOH was evaporated under reduced pressure to afford the title compound 299 (88 mg, 0.24 mmol, 60% yield), which was used without purification. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.24 (s, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 6.6 Hz, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.31-7.10 (m, 3H), 7.06-6.94 (m, 1H), 4.12 (dd, J = 7.5, 4.5 Hz, 1H), 3.74 (dd, J = 7.8, 5.4 Hz, 1H), 3.64-3.51 (m, 1H), 2.64 (s, 3H), 1.49 (s, 9H).

Step 3: (2-{4-[1-(3,4-Dimethoxy-benzoylamino)-2-hydroxy-ethyl]-benzoylamino}-phenyl)-carbamic acid tert-butyl ester (300)

[0364] To a stirred solution of 299 (88 mg, 0.24 mmol) in dry DCM (2 mL) at -20°C was added 3,4-dimethoxybenzoyl chloride (50 mg, 0.25 mmol) followed by Et₃N (37 μL, 0.26 mmol). The reaction mixture was allowed to warm up to room temperature then was stirred for 48 h. A solution of sat. NH₄Cl was added, followed by DCM and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 4/96) to afford title compound 300 (91 mg, 0.17 mmol, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 9.29 (s, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.65-7.58 (m, 1H), 7.46 (m, 7H), 6.80 (d, J = 8.1 Hz, 1H), 5.20-5.10 (m, 1H), 3.95-3.78 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 1.47 (s, 9H).

Step 4: N-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-4-yl]-benzamide (301)

[0365] To a solution of 300 (91 mg, 0.17 mmol) in dry THF (2 mL) was added the Burgess reagent (44 mg, 0.19 mmol) and the mixture was stirred at 70°C for 2 h. The reaction mixture was partitioned between AcOEt and water and the phases were separated. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude residue was purified by flash chromatography on silica gel (MeOH/DCM: 3/97) to afford the Boc-protected intermediate (75 mg, 0.14 mmol, 85% yield). ¹H NMR (CDCl₃) δ (ppm): 9.31 (s, 1H), 7.94 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 7.5

Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 6.0 Hz, 1H), 7.23-7.08 (m, 3H), 6.93 (d, J = 8.7 Hz, 1H), 5.43 (t, J = 9.0 Hz, 1H), 4.84 (t, J = 9.3 Hz, 1H), 4.26 (t, J = 8.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.50 (s, 9H).

[0366] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for 46, the title compound 301 was obtained in 82%. ¹H NMR (CDCl₃) δ (ppm): 8.01 (s, 1H), 7.89 (d, J = 7.9 Hz, 2H), 7.65 (dd, J = 8.4, 1.5 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 1H), 7.08 (t, J = 6.6 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 2H), 5.43 (dd, J = 9.7, 8.4 Hz, 1H), 4.83 (dd, J = 9.7, 8.4 Hz, 1H), 4.25 (t, J = 8.1 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H).

Example 173

Step 1: {2-[4-(2-Amino-1-hydroxy-ethyl)-benzoylamino]-phenyl}-carbamic acid tert-butyl ester (303)

[0367] The title compound 303 was obtained in 94% yield from 302 following the same procedure as in Example 172, step 2. The compound 303 was used directly for next step without purification.

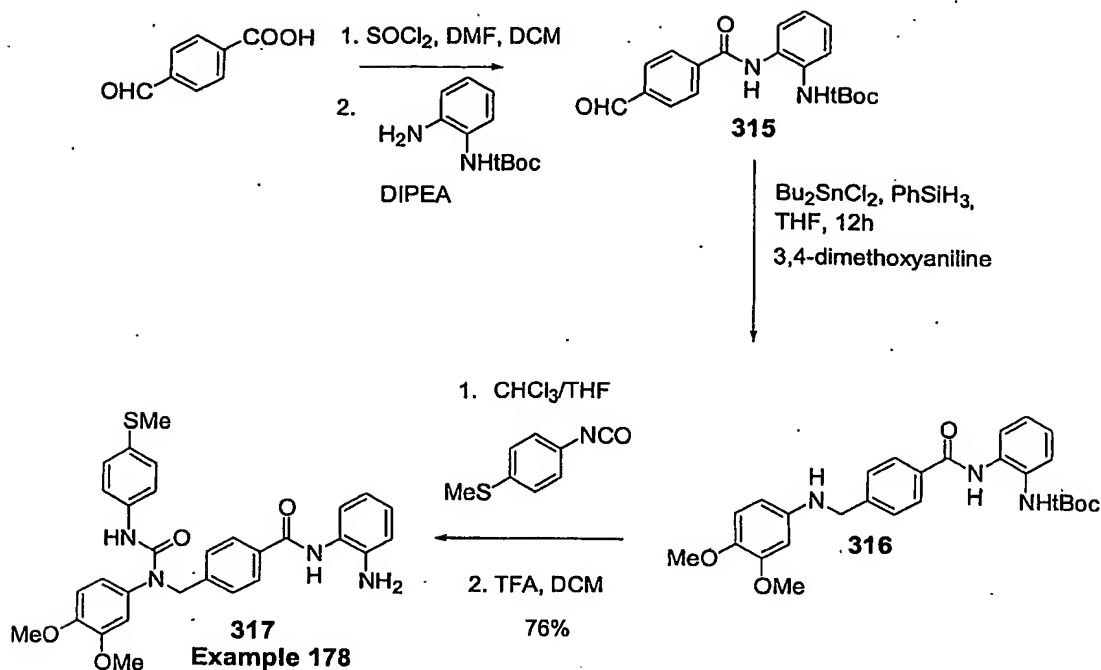
Step 2: 2-{4-[2-(3,4-Dimethoxy-benzoylamino)-1-hydroxy-ethyl]-benzoylamino}-phenyl}-carbamic acid tert-butyl ester (304)

[0368] The title compound 304 was obtained in 40% yield from 303 and 3,4-dimethoxybenzoyl chloride following the same procedure as in Example 172, step 3. ¹H NMR (CDCl₃) δ (ppm): 9.31 (s, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 6.9 Hz, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 8.1 Hz), 7.30-7.06 (m, 4H), 7.00-6.93 (m, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.89-4.82 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.85-3.73 (m, 1H), 3.44-3.32 (m, 1H), 1.46 (s, 9H).

Step 3: N-(2-Amino-phenyl)-4-[2-(3,4-dimethoxy-phenyl)-4,5-dihydro-oxazol-5-yl]-benzamide (305)

[0369] Following a procedure analogous to that described in Example 172, step 4, 5, but substituting 304 for 300, the title compound 305 was obtained in 63%. ¹H NMR (CDCl₃) δ (ppm): 8.02 (s, 1H), 7.93 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 8.4, 1.8 Hz, 1H), 7.60 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.5 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.1 Hz, 2H), 5.74 (dd, J = 10.0, 7.8 Hz, 1H), 4.51 (dd, J = 14.5, 10.0 Hz, 1H), 4.00-3.90 (m, 7H).

Scheme 57



Example 178

STEP 1: [2-(4-FORMYL-BENZOYLAMINO)-PHENYL]-CARBAMIC ACID *TERT*-BUTYL ESTER (315)

[0370] To a suspension of 4-carboxybenzaldehyde (6 g, 40 mmol) in dichloromethane (10 mL) was added thionyl chloride (4.1 mL, 56 mmol, 1.4 eq), followed by DMF (1 mL) dropwise. The mixture was refluxed for 4 hours and excess of thionyl chloride and DMF were removed under reduced pressure. To a solution of (2-aminophenyl)-carbamic acid *tert*-butyl ester (8.32 g, 40 mmol, 1 eq) in dichloromethane (80 mL), stirred at 0°C, was added a suspension of 4-formyl benzoyl chloride in dichloromethane (20 mL), followed by diisopropyl ethylamine (3.61 mL, 20 mmol, 1 eq). The mixture was stirred for 30 minutes at 0°C then at room temperature for 30 minutes. The crude residue was diluted with dichloromethane (300 mL) and washed with water. The combined organic layers were dried (MgSO₄), filtered and concentrated under vacuo. The crude residue was purified by column chromatography on silica gel (elution 20% ethyl acetate in hexane) to give 6.1 g (45% yield) of anilide 315. ¹H NMR (CDCl₃): δ 10.18 (s, 1H), 9.64 (brs, 1H), 8.20 (d, J = 7.9 Hz, 2H), 8.06 (d, J = 7.9 Hz, 2H), 7.96 (d, J = 7.9 Hz, 1H), 7.28-7.38 (m, 1H), 7.24 (d, J = 4.4 Hz, 1H), 6.84 (s, 1H), 6.81 (d, J = 8.8 Hz, 1H), 1.58 (s, 9H).

Step 2: (2-{4-[(3,4-Dimethoxyphenylamino)-Methyl]-Benzoylamino}-Phenyl)-Carbamic Acid Tert-Butyl Ester (316)

[0371] Following a procedure analogous to that described in Example 144, step 3, but substituting the previous compound for 226, the title compound 316 was obtained in quantitative yield. ¹H NMR

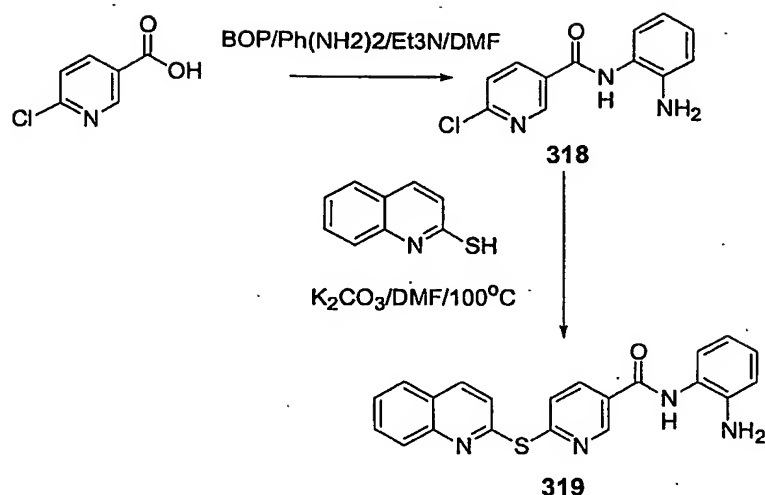
(CDCl₃): δ 9.21 (brs, 1H), 8.01 (d, J = 7.9 Hz, 2H), 7.86 (d, J = 7.0 Hz, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.20-7.34 (m, 3H), 6.89 (brs, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 6.23 (dd, J = 2.6, 8.3 Hz, 1H), 4.45 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 1.58 (s, 9H).

Step 3: N-(2-Aminophenyl)-4-[1-(3,4-dimethoxyphenyl)-3-(4-methylsulfonylphenyl)-ureidomethyl]-benzamide 317

[0372] To a solution of anilide 316 (500 mg, 1.047 mmol) in chloroform/THF (1:1, 10 mL) was added isocyanate (169 μL, 1.205 mmol, 1.15 eq). The mixture was stirred overnight at room temperature under nitrogen and the crude residue was concentrated and purified by column chromatography on silica gel (elution 40% ethyl acetate in hexane) to give 606 mg (90% yield) of the desired compound. ¹H NMR (CDCl₃): δ 9.25 (s, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.85 (d, J = 7.0 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.20-7.36 (m, 6H), 6.93 (d, J = 3.5 Hz, 1H), 6.90 (s, 1H), 6.75 (dd, J = 2.2, 8.3 Hz, 1H), 6.68 (dd, J = 2.6 Hz, 1H), 6.33 (s, 1H), 5.0 (s, 2H), 3.97 (s, 3H), 3.85 (s, 3H), 2.51 (s, 3H), 1.57 (s, 9H).

[0373] Following a procedure analogous to that described in Example 42, step 3, but substituting the previous compound for 46, the title compound 317 was obtained in 85% yield. ¹H NMR (DMSO-d₆): δ 10.14 (brs, 1H), 7.99 (d, J = 7.9 Hz, 2H), 7.93 (s, 1H), 7.49 (d, J = 8.35 Hz, 4H), 7.39 (d, J = 7.5 Hz, 1H), 7.10-7.30 (2m, 5H), 6.97 (dd, J = 2.2, 8.35 Hz, 1H), 6.77 (dd, J = 2.2, 8.35 Hz, 1H), 5.02 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.48 (s, 3H).

Scheme 58



Example 179

Example 179

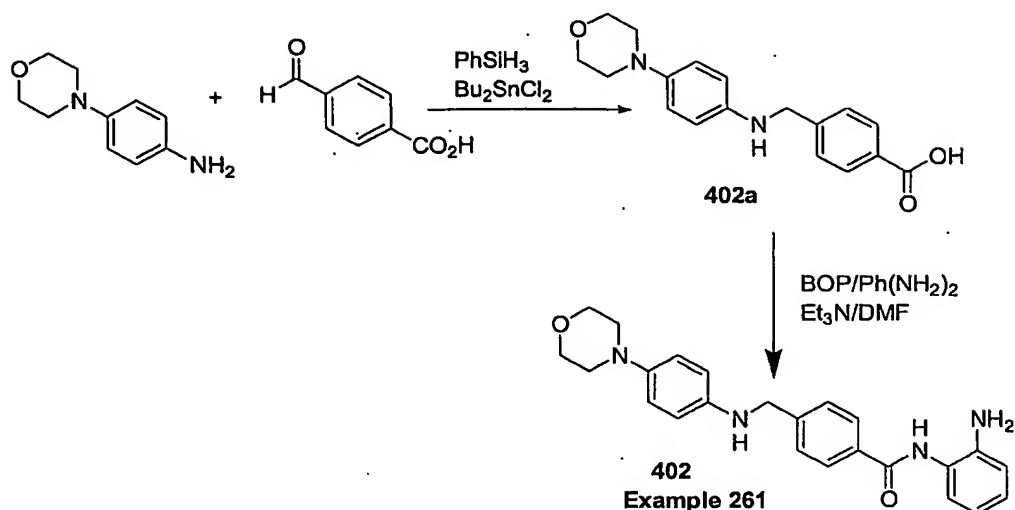
Step 1: N-(2-Amino-phenyl)-6-chloro-nicotinamide (318)

[0374] Following the procedure described in Example 42, step 2, the title compound 318 was obtained in 80% yield. LRMS = calc:246.69, found:247.7.

Step 2: N-(2-Amino-phenyl)-6-(quinolin-2-ylsulfanyl)-nicotinamide (319)

[0375] Following the procedure described in Example 45, step 1 but substituting 318 for 3,4,5-trimethoxybenzylamine, the title compound 319 was obtained in 20% yield. ¹H NMR: (CD₃OD-d₆) δ (ppm): 9.08 (d, J= 1.9 Hz, 1H), 8.35-8.25 (m, 2H), 7.99-7.56 (m, 7H), 7.23 (dd, J = 1.2, 7.9 Hz, 1H), 7.12 (dd J=1.4, 7.9, 14.0 Hz, 1H), 6.93 (dd, J=1.2, 8.0Hz, 1H), 6.79 (ddd, J=1.4, 7.7, 13.7 Hz, 1H).

Scheme 59



Step 1: 4-[(4-Morpholin-4-yl-phenylamino)-methyl]-benzoic acid (402a).

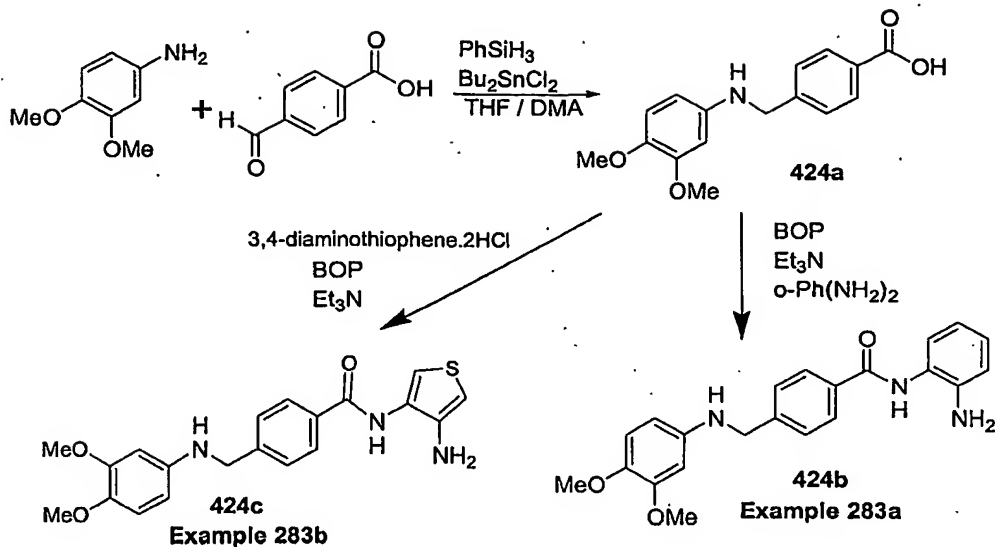
[0376] A suspension of 4-formylbenzoic acid (2.53g; 16.8 mmol; 1 eq), 4-morpholinoaniline (3g; 16.8 mmol; 1 eq) and Bu_2SnCl_2 (510 mg; 1.68 mmol; 0.1 eq) in dry THF (20 ml) was treated with PhSiH_3 (3.31ml; 16.8 mmol; 1 eq) at room temperature for 12 h. The reaction was filtered and the solid product was washed with MeOH. The yield of the reaction was 5.25g (99%). LRMS: calc 312.37; found: 313.2.

Step 2: N-(2-Amino-phenyl)-4-[(4-morpholin-4-yl-phenylamino)-methyl]-benzamide (402)

[0377] To a solution of acid 402a (2.61g; 8.36 mmol; 1 eq), 1,2-phenylenediamine (903 mg; 8.36 mmol; 1 eq) and BOP (3.70g; 8.36 mmol; 1 eq) in dry DMF (20 ml) was added Et_3N (4.64ml; 33.4 mmol; 4 eq). After stirring overnight most of the DMF was removed under reduced pressure and chromatographed (Hex:EtAcO: 1:2/ EtAcO). The crystal 402 was obtained in 70% (2.35g). $^1\text{H-NMR}$ (300.07 MHz; DMSO-d_6) δ (ppm): 9.65 (s, 1H), 7.97 (d, $J=7.9$, 2H), 7.53 (d, $J=7.9$, 2H), 7.22 (d, $J=7.5$, 1H), 7.03 (dd, $J=7.0$, 7.5, 1H), 6.83 (d, $J=7.9$, 1H), 6.77 (d, $J=8.8$, 2H), 6.65 (dd, $J=7.5$, 7.0, 1H), 6.57 (d, $J=8.8$, 2H), 4.93 (bs, 2H), 4.36 (d, $J=5.7$, 2H), 3.75 (m, 4H), 2.93 (m, 4H).

LRMS: calc 402.49; found: 403.4.

Scheme 60



Example 283a

Step 1. 4-[(3,4-Dimethoxyphenylamino)-methyl]-benzoic acid (424a)

[0378] In a 50 ml flask, a mixture of 4-aminoveratrole (1.53 g, 10 mmol), 4-formyl-benzoic acid (1.50 g, 10 mmol), dibutyltin dichloride (304 mg, 1 mmol), phenylsilane (2.47 ml, 20 mmol) in anhydrous THF (10 mL) and DMA (10 ml) was stirred overnight. at room temperature. After solvents removal, the crude residue was dissolved in ethyl acetate (100 ml) and then washed with saturated aqueous solution of NaHCO_3 (50 ml x 3) . The combined aqueous layers were acidified with 6% of NaHSO_4 to pH = 4. The resulting white suspension was filtrated and then the filter cake was washed with water (5 ml x 3). The cake was dried over freeze dryer to afford acid (1.92 g, 67 %) white solid product. LRMS = 288 (MH)⁺.

Step 2. N-(2-Aminophenyl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide (424b)

[0379] In a 150 ml flask, a mixture of acid (1.92 g, 6.69 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP, 3.26 g, 7.37 mmol), triethylamine (1.87 ml, 13.4 mmol), o-phenylenediamine (1.30g, 12.02 mmol) in methylenechloride (67 ml) was stirred at rt for 2 h. After solvents removal, the crude residue was dissolved in EtOAc (100 ml) and then washed with NaHCO_3 saturated solution and brine 50 ml. The combined organic layers were dried over Na_2SO_4 and the filtrate was concentrated to dryness. The crude material was submitted to a chromatographic purification (column silica, 55%-70 % EtOAc in 1%

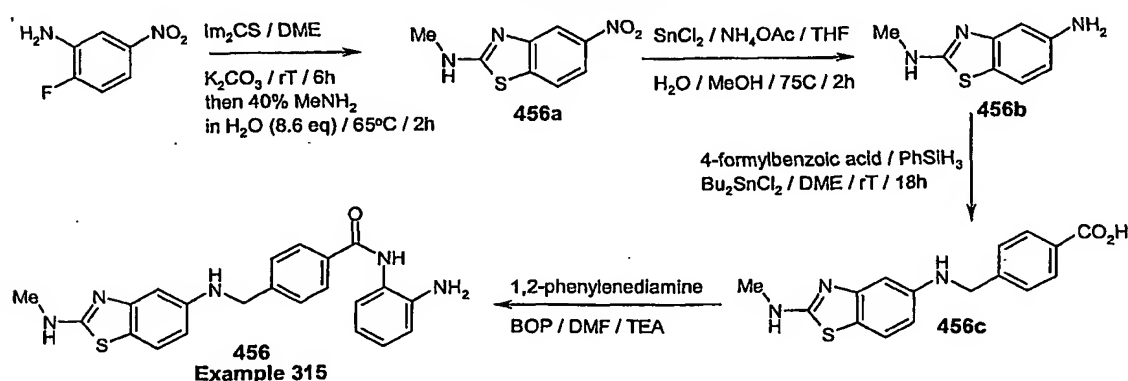
Et₃N of hexanes) and then the all interested fractions were concentrated to dryness. The residue was suspended in minimum quantities of ethyl acetate and then filtered to afford final product (1.49 g, 59 %). ¹H NMR (300 MHz, DMSO-d₆) δ (ppm): 9.65 (s, 1H), 7.98 (d, J = 7.9 Hz, 2H), 7.54 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 7.9 Hz, 1H), 7.02 (dd, J = 7.9, 7.9 Hz, 1H), 6.83 (d, J = 7.9 Hz, 1H), 6.72 (d, J = 8.79 Hz, 1H), 6.45 (dd, J = 7.5, 7.5 Hz, 1H), 6.39 (d, J = 2.2 Hz, 1H), 6.01-6.08 (m, 2H), 4.94 (s, 2H, NH₂), 4.36 (d, J = 6.16 Hz, 2H), 3.72 (s, 3H), 3.65 (s, 3H).

Example 283b

Step 1: N-(4-Aminothiophen-3-yl)-4-[(3,4-dimethoxyphenylamino)-methyl]-benzamide:

[0380] Acid 424a (1040 mg; 3.62 mmol); 3,4-diaminothiophene dihydrochloride (1017 mg; 5.44 mmol; 1.50 eq.) and BOP (1770 mg; 4.0 mmol; 1.1 eq.) were suspended in MeCN, treated with triethylamine (4 mL; 29 mmol) and stirred for 18h at room temperature; concentrated and purified by chromatographic column on silica gel (elution 50% EtOAc in DCM) to render 527 mg (1.37 mmol; 38 % yield) of compound 424c which was 90% pure. ¹H-NMR (300.07 MHz; DMSO-d₆) δ (ppm): 8.56 (s, 1H), 7.78 (d, J=7.9 Hz, 2H), 7.43 (d, J = 3.5 Hz, 1H), 7.38 (d, J = 7.9 Hz, 2H), 6.73 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 3.5 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 6.13 (dd, J = 2.6, 8.3 Hz, 1H), 4.33 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H). LRMS: calc: 383.4642; found: 384.2 (M+H); 406.2 (M+Na) and 192.6 (M+2H)/2.

Scheme 61



Step 1: Methyl-(5-nitrobenzothiazol-2-yl)-amine (456a)

[0381] A mixture of 2-fluoro-5-nitroaniline (861 mg; 5.52 mmol; 1.02 eq); Im₂CS (960.3 mg; 5.39 mmol) and dry K₂CO₃ (1.45g) was

suspended in dry DME (10 mL) and stirred under nitrogen for 90 min at room temperature. The yellow suspension was made fluid by diluting with DME (10 mL) followed by addition of 40% MeNH₂ in water (4.0 mL; 46.5 mmol; 8.6 eq). The system was heated up to 65°C and stirred at this temperature for 3.5 h, cooled down, diluted with ethyl acetate and washed with saturated NaCl (X2). After conventional work-up procedures, the dark crude mixture was purified through chromatographic column on silica gel (elution 50% EtOAc in hexane, then 5% MeOH in DCM), to afford 836.8 mg (4.0 mmol; 72% yield) of compound 456a.

Step 2: N-Methyl-benzothiazole-2,5-diamine (456b)

[0382] A mixture of nitro compound 456a (593 mg; 2.83 mmol); SnCl₂ (4.02 g; 20.8 mmol; 7.35 eq) and NH₄OAc (4.5g) was suspended in THF:MeOH:H₂O = 1:1:1 (60 mL) and stirred at 70°C for 2 h, cooled down, diluted with ethyl acetate and successively washed with saturated NaHCO₃ and brine; dried (MgSO₄) filtered and concentrated. The residue (443 mg; 2.43 mmol; 87%) showed consistent spectrum and suitable purity degree for synthetic purposes, therefore was submitted to the next step without further purification.

Step 3: 4-[(2-Methylaminobenzothiazol-5-Ylamino)-Methyl]-Benzoic Acid (456c)

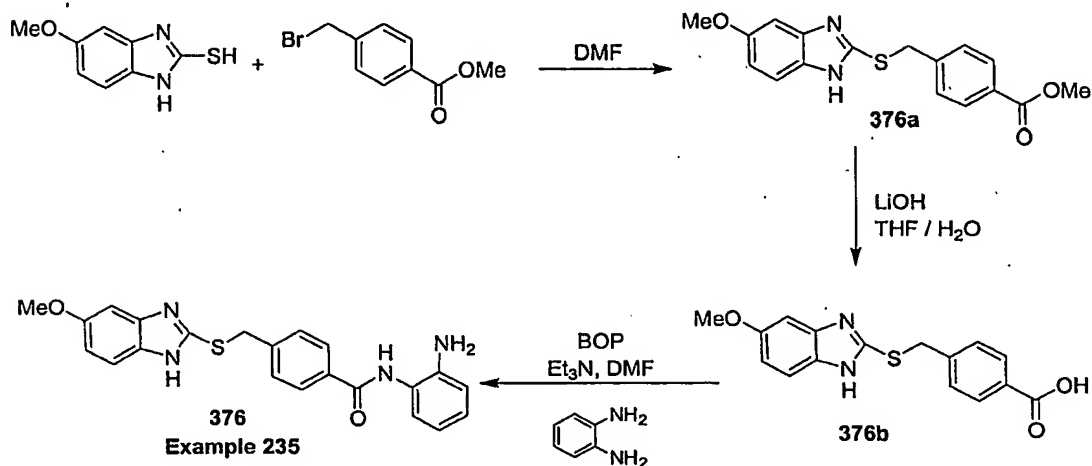
[0383] A solution of aniline 456b (509 mg; 2.8 mmol); 4-formylbenzoic acid (426 mg; 2.8 mmol) and Bu₂SnCl₂ (198 mg; 0.65 mmol; 23% mol) in DME (14 mL) was stirred at room temperature for 3 min and treated with neat PhSiH₃ (0.6 mL; 4.7 mmol; 1.7 mmol) and allowed to react for 18h. After quenching the excess of silane with MeOH, the mixture was concentrated and purified by chromatographic column on silica gel (elution 5% MeOH in DCM) to give 729 mg (2.54 mmol; 91% yield) of acid 456c.

Step 4: N-(2-Aminophenyl)-4-[(2-methylaminobenzothiazol-5-ylamino)-methyl]-benzamide (456)

[0384] A mixture of acid 456c (729 mg; 2.54 mmol), 1,2-phenylenediamine (376 mg; 3.47 mmol; 1.36 eq) and BOP (1.43 g; 3.23 mmol; 1.27 eq) was dissolved in acetonitrile (15 mL), treated with triethylamine (3mL) and stirred overnight. The reaction mixture was quenched with methanol, concentrated and purified by chromatographic column on silica gel (40% EtOAc in DCM) and the obtained material crystallized from DCM to give 358 mg (0.88 mmol; 35 % yield) of pure

compound 456. $^1\text{H-NMR}$ (300 MHz; $\text{DMSO-}d_6$) δ (ppm): 9.57 (s, 1H), 7.92 (d, $J = 7.9$ Hz, 2H), 7.66 (d, $J = 4.8$ Hz, 1H), 7.48 (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.3$ Hz, 1H), 7.15 (d, $J = 7.9$ Hz, 1H), 6.95 (t, $J = 7.5$ Hz, 1H), 6.76 4.87 (bs, 2H), 6.58 (t, $J = 7.5$ Hz, 1H), 6.54 (d, $J = 1.8$ Hz, 1H), 6.13 (dd, $J = 1.8, 8.3$ Hz, 1H), 6.27 (t, $J = 5.7$ Hz, 1H), 4.87 (bs, 2H), 4.36 (d, $J = 5.7$ Hz, 2H), 2.85 (d, $J = 4.8$ Hz, 3H). LRMS: calc: 403.5008, found: 404.2 ($\text{M}+\text{NH}$) and 202.6 ($\text{M}+2\text{H}$)/2.

Scheme 62



Example 235

Step 1: Methyl-4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoate (376a)

[0385] To a solution 5-methoxy-2-thiobenzimidazole (2.00 g, 11.1 mmol) of in anhydrous DMF (40 ml) was added methyl-4-(bromomethyl)-benzoate (2.54 g, 11.1 mmol). The reaction mixture was stirred 16 h at room temperature. The DMF was evaporated and the residue was triturated in ethyl acetate during 30 min and then filtered and dried. The desired compound was isolated as the HBr salt: 98% yield, (4.44 g). $^1\text{H NMR}$: (DMSO) δ (ppm): 7.90 (d, $J = 8.8$ Hz, 2H), 7.56-7.52 (m, 3H), 7.09 (d, $J = 2.2$ Hz, 1H), 7.01 (dd, $J = 8.8, 2.2$ Hz, 1H), 4.73 (s, 2H), 3.82 (s, 6H). MS: (calc.) 328.1, (obt.), 329.2 (MH)⁺.

Step 2: 4-(5-Methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid (376b)

[0386] A solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.02 g, 24.4 mmol) in water (15 ml) was added to a suspension of 376a (3.99 g, 9.75 mmol) of in THF (10

ml). The reaction mixture was stirred 16 h at room temperature. The reaction mixture was acidified with a solution of HCl 1 M to pH 4. The desired product was triturated 20 min. at 0°C and then filtered and dried. Compound **376b** was obtained as a white powder (100% yield, 3.05 g). ¹H NMR: (DMSO) δ (ppm): 12.85 (bs, 1H), 7.86 (d, J = 8.1 Hz, 2H), 7.53 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.76 (dd, J = 8.8, 2.2 Hz, 1H), 4.60 (s, 2H), 3.82 (s, 3 H). MS: (calc.) 314.1, (obt.), 315.1 (MH)+.

Step 3: N-(2-Amino-phenyl)-4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzamide (376)

[0387] Following the procedure described in Example 1 step 5 but substituting 4-(5-methoxy-1H-benzimidazol-2-yl-sulfanylmethyl)-benzoic acid 2 for 7 the title compound **376** was obtained as a white powder.: 36% yield (933 mg). ¹H NMR: (DMSO) δ (ppm): 12.42 (bs, 1H), 9.57 (bs, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 7.3 Hz, 1H), 6.98-6.93 (m, 2H), 6.77-6.55 (m, 2H), 6.58 (dd, J = 7.3, 7.3 Hz, 1H), 4.87 (s, 2H), 4.59 (s, 2H), 3.77 (s, 3 H). MS: (calc.) 404.1, (obt.), 405.4 (MH)+.

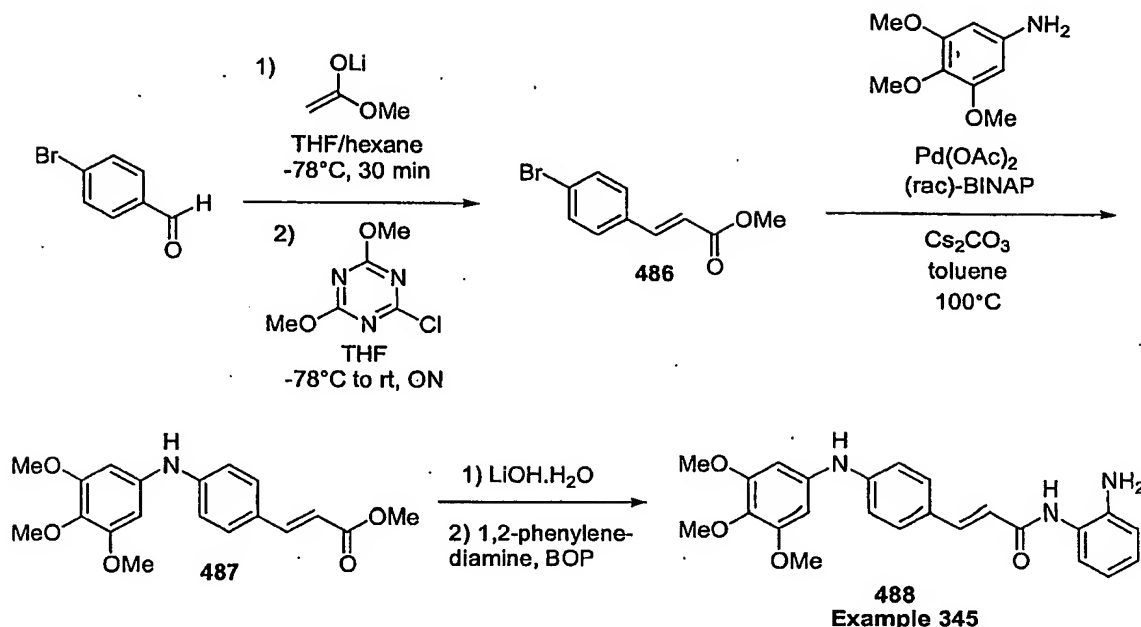
Examples 180-328

[0388] Examples 180 to 327 (compounds 320 - 468) were prepared using the same procedure as described for compound 126 to 319 in Example 85 to 179 (scheme 11 to 58).

Examples 329-344

[0389] Examples 329 to 344 (compounds 470 - 485) were prepared using the same procedure as described for compound 8 to 224 in Example 1 to 143 (scheme 1 to 32).

Scheme 63



Example 345

Step 1: Methyl 3-(4-bromo-phenyl)-acrylic ester (486)

[0390] To a solution of anhydrous $i\text{-Pr}_2\text{NH}$ (758 μl , 5.40 mmol) in anhydrous THF (25 ml) stirred at 0°C under nitrogen, was slowly added a solution of $n\text{-BuLi}$ (2.22 ml, 5.54 mmol, 2.5 M in hexane). After 30 min, LDA was cooled to -78°C and anhydrous methyl acetate (430 μl , 5.40 mmol) was added dropwise. After 30 min, a solution of 4-bromobenzaldehyde (500 mg, 2.70 mmol) in anhydrous THF (10 ml) was slowly added. After 30 min, a solution of 2-chloro-4,6-dimethoxy-1,3,5-triazine (569 mg, 3.24 mmol) in anhydrous THF (15 ml) was added. Then, the temperature was allowed to warm up to room temperature overnight. A suspension appeared. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl , and diluted with AcOEt . After separation, the organic layer was successively washed with H_2O and brine, dried over MgSO_4 , filtered and concentrated. The crude product was purified by flash chromatography on silica gel (AcOEt /hexane: 10/90) to give the title product 486 (394 mg, 1.9 mmol, 61% yield) as a colorless crystalline solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.63 (d, $J = 16.2$ Hz, 1H), AB system ($\delta_A = 7.53$, $\delta_B = 7.39$, $J = 8.4$ Hz, 4H), 6.43 (d, $J = 15.8$ Hz, 1H), 3.82 (s, 3H).

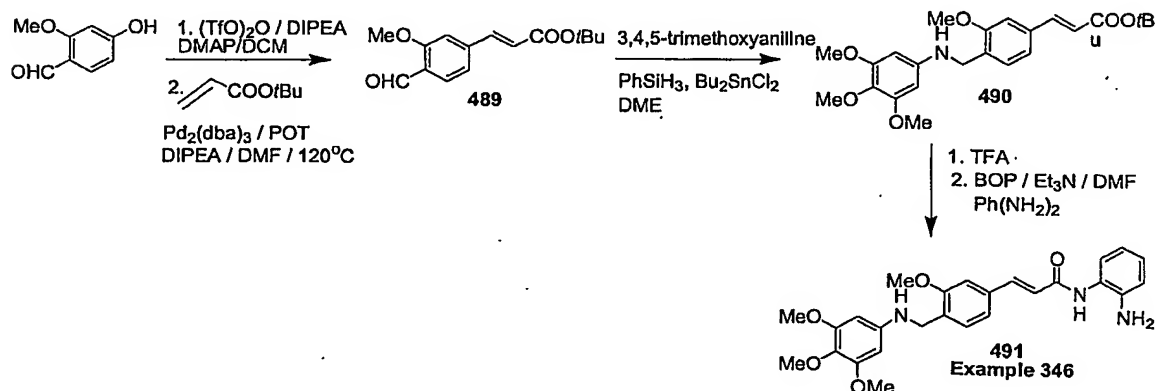
Step 2: Methyl 3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylic ester (487)

[0391] A mixture of Cs_2CO_3 (378 mg, 1.16 mmol), $\text{Pd}(\text{OAc})_2$ (6 mg, 0.025 mmol), (rac)-BINAP (23 mg, 0.037 mmol), was purged with nitrogen for 10 min. 486 (200 mg, 0.83 mmol), 3,4,5-trimethoxyaniline (182 mg, 0.99 mmol), and anhydrous toluene (5 ml) were added, respectively. The reaction mixture was heated to 100°C under nitrogen for 24 h. Then, it was allowed to cool to room temperature, diluted with AcOEt, and successively washed with a saturated aqueous solution NaHCO_3 , H_2O , sat. NH_4Cl , H_2O and brine, dried over anhydrous MgSO_4 , filtered and concentrated. The crude residue was then purified by flash chromatography on silica gel (AcOEt/hexane: 40/60) to afford the title compound 487 (280 mg, 0.82 mmol, 98% yield) as a yellow oil. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.64 (d, $J = 16.2$ Hz, 1H), 7.43 (bd, $J = 7.9$ Hz, 2H), 7.12-6.86 (m, 2H), 6.60-6.20 (m, 3H, included at 6.29, d, $J = 15.8$ Hz), 3.84 (s, 9H), 3.80 (s, 3H).

Step 3: N-(2-Amino-phenyl)-3-[4-(3,4,5-trimethoxy-phenylamino)-phenyl]-acrylamide (488)

[0392] The title compound 488 was obtained from 487 in 2 steps following the same procedure as Example 1, steps 4 and 5. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ (ppm): 9.29 (s, 1H), 8.48 (s, 1H), 7.60-7.42 (m, 3H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.94 (t, $J = 7.5$ Hz, 1H), 6.78 (d, $J = 7.9$ Hz, 1H), 6.71 (d, $J = 15.8$ Hz, 1H), 6.61 (t, $J = 7.1$ Hz, 1H), 6.47 (s, 2H), 4.97 (s, 2H), 3.79 (s, 6H), 3.66 (s, 3H).

Scheme 64



Example 346

Step 1: 3-(4-Formyl-3-methoxy-phenyl)-acrylic acid tert-butyl ester 489

[0393] Following the procedure described in Example 53, step 1, but substituting 4-hydroxy-2-methoxy-benzaldehyde for 84, followed by Example 42, step 2, but substituting the previous compound for 42, the title compound 489 was obtained in 29% yield. LRMS = calc: 262, found: 263.2 (M+H⁺).

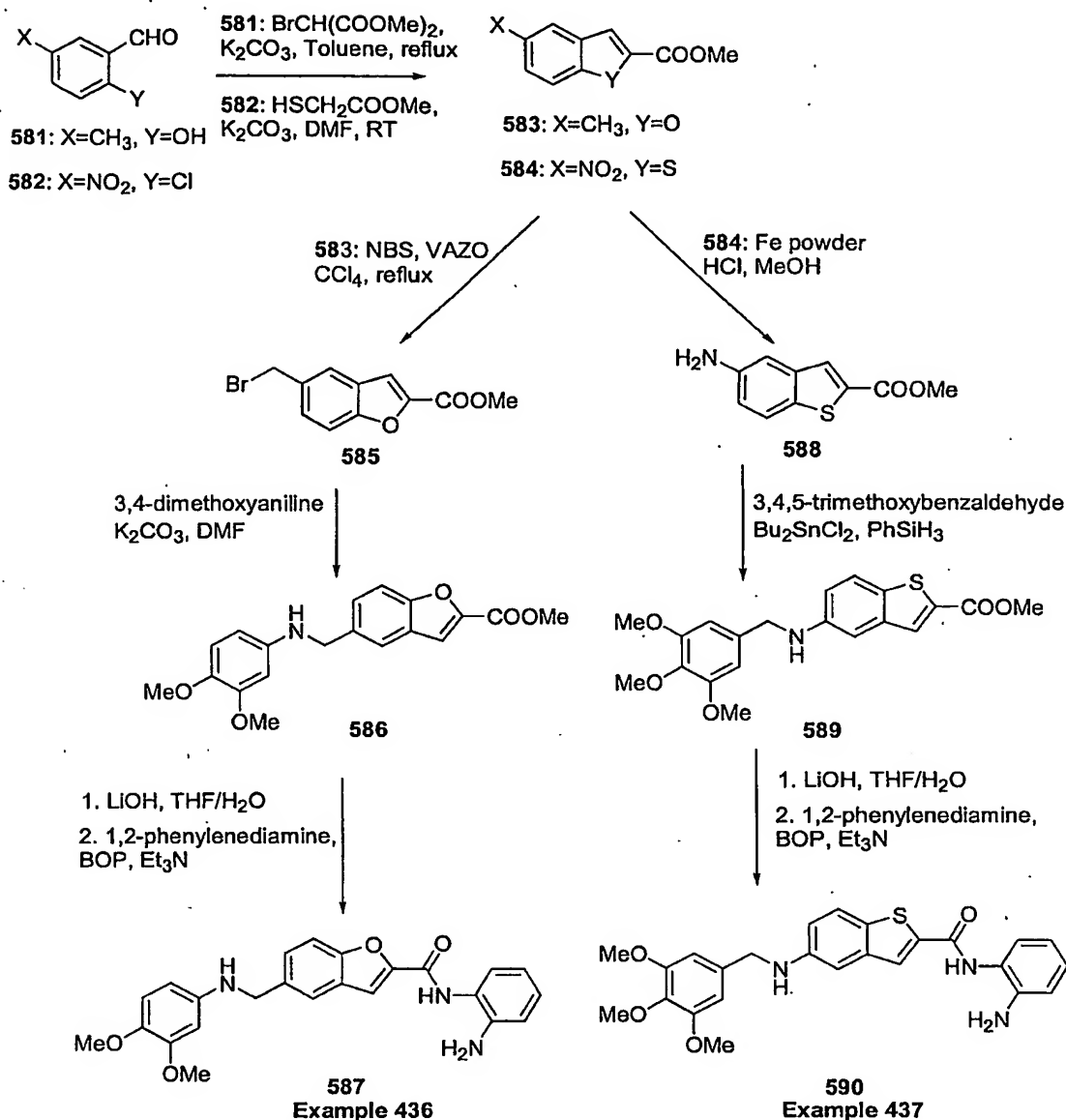
Step 2: 3-{3-Methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylic acid tert-butyl ester 490

[0394] Following the procedure described in Example 144, step 3, but substituting 489 for 4-formylbenzaldehyde, the title compound 490 was obtained in 69% yield. LRMS = calc: 429, found: 430.5 (M+H⁺).

Step 3: N-(2-Amino-phenyl)-3-{3-methoxy-4-[(3,4,5-trimethoxy-phenylamino)-methyl]-phenyl}-acrylamide 491

[0395] Following the procedure described in Example 42, step 3, 4, but substituting 490 for 46, the title compound 491 was obtained in 67% yield. ¹H NMR (CDCl₃), δ (ppm): 8.08 (s, 1H), 7.74 (d, J = 15.4 Hz, 1H), 7.30 (m, 1H), 7.06 (m, 3H); 6.80 (m, 3H), 6.70 (d, J = 15.4 Hz, 1H), 5.98 (s, 2H), 4.40 (s, 2H); 4.12 (bs, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 3.77 (s, 6H).

Scheme 65



Example 436

Step 1: Methyl-5-methyl-benzofuran-2-carboxylate (583)

[0396] A stirring suspension of 5-methylsalicylaldehyde (1.0 mg, 7.5 mmol), K_2CO_3 (1.55 g, 11.0 mmol), and Bu_4NBr (322 mg, 1 mmol) in toluene (30ml) was treated with dimethylbromomalonate (1.06 ml, 8.0 mmol). The suspension was heated to reflux with a Dean-Stark trap for 20 h. The brown suspension was cooled to 25°C and concentrated in vacuo. The residue was taken in DCM and filtered. The filtrate was washed with H_2O , 1N NaOH and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude residue was

purified by column chromatography (10% ethyl acetate/hexane) to afford the title compound **583** (600mg, 42% yield). LRMS : 190.2 (Calc.); 191.1 (found).

Step 2: Methyl-5-bromomethyl-benzofuran-2-carboxylate (585)

[0397] A mixture of **583** (500 mg, 2.63 mmol), *N*-bromosuccinimide (561 mg, 3.15 mmol) and 1,1'-azobis(cyclohexanecarbonitrile) (Vazo) (63 mg, 0.26 mmol) in 15 ml of CCl₄ was heated overnight under reflux. The mixture was cooled to room temperature, quenched by adding water and extracted with DCM. The organic layer was washed with brine and dried over MgSO₄, filtered and concentrated. The crude residue was purified by column chromatography (30% ethyl acetate/hexane) to afford the title compound **585** (680mg, 96% yield). ¹H NMR: (CDCl₃) δ (ppm): 7.79 (s, 1H), 7.70-7.52 (m, 3H), 4.69 (s, 2H), 4.06 (s, 3H), 3.72 (s, 2H). LRMS : 268.2 (Calc.); 269.1 (found).

Step 3: Methyl-5-[(3,4-dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylate (586)

[0398] Following the procedure described in Example 47, step 2, but substituting **585** for **63**, the title compound **586** was obtained in 40% yield. LRMS : 341 (Calc.); 342.3 (found).

Step 4: 5-[(3,4-Dimethoxy-phenylamino)-methyl]-benzofuran-2-carboxylic acid (2-amino-phenyl)-amide (587)

[0399] Following the procedure described in Example 1, steps 4,5, but substituting **585** for **6**, the title compound **587** was obtained in 29% yield. ¹H NMR: (DMSO) δ (ppm): 9.83 (s, 1H), 7.75 (s, 1H), 7.64 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 9.0 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.59 (t, J = 7.5 Hz, 1H), 6.33 (s, 1H), 6.04 (d, J = 8.0 Hz, 1H), 5.92 (d, J = 5.5 Hz, 1H), 4.93 (s, 2H), 4.31 (d, J = 5.5 Hz, 1H), 2.82 (s, 3H), 2.76 (s, 3H). LRMS : 417.46 (Calc.); 418.4 (found).

Example 437

Step 1: Methyl-5-nitro-benzo[b]thiophene-2-carboxylate (584)

[0400] A stirring suspension of 5-nitro-2-chloro-benzaldehyde (4.0 g, 21.6 mmol) in DMF (40 ml) at 5°C was treated with K₂CO₃ (3.52 g, 25.5 mmol) followed by methylglycolate (1.93 ml, 21.6 mmol). The resulting solution was warmed to 25°C and stirred for 20h. The

solution was then poured into 250ml of ice H₂O and the white precipitate that formed was collected by filtration. Crystallization from EtOAc afforded fine pale orange needles of **584** (3.54 g, 69%).

LRMS : 237.0 (Calc.); 238.1 (found). ¹H NMR: (DMSO) δ (ppm): 9.00 (d, J = 2.2 Hz, 1H), 8.45 (s, 1H), 8.39-8.30 (m, 2H), 3.93 (s, 3H).

Step 2: Methyl-5-amino-benzo[b]thiophene-2-carboxylate (**588**)

[0401] A suspension of **584** (3.52 g, 14.8 mmol) in methanol (100 ml) was treated with Fe powder (6.63 g, 118.7 mmol). The resulting suspension was heated to reflux, and 12M HCl (8.5 ml) was slowly added over 15 min. The resulting green dark suspension was refluxed for an additional 3 h, then cooled and concentrated. The residue was taken up in EtOAc and washed with saturated aqueous NaHCO₃, then brine, dried over MgSO₄, filtered and concentrated to afford (2.57 g, 84%). ¹H NMR: (DMSO) δ (ppm): 7.92 (s, 1H), 7.65 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.88 (dd, J = 1.8, 8.4 Hz, 1H), 5.27 (s, 2H), 3.85 (s, 3H). LRMS : 207.0 (Calc.); 208.1 (found).

Step 3: Methyl-5-(3,4,5-trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylate (**589**)

[0402] Following the procedure described in Example 144, step 3, but substituting **588** for **226**, the title compound **589** was obtained in 68% yield. (DMSO) δ (ppm): 7.94 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.02-6.99 (m, 2H), 6.73 (s, 2H), 6.41 (t, J = 5.7 Hz, 1H), 4.21 (d, J = 5.9 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 6H), 3.62 (s, 3H). LRMS : 387.1 (Calc.); 388.3 (found).

Step 4: 5-(3,4,5-Trimethoxy-benzylamino)-benzo[b]thiophene-2-carboxylic acid (2-amino-phenyl)-amide (**590**)

[0403] Following the procedure described in Example 1, steps 4,5, but substituting **589** for **6**, the title compound **590** was obtained in % yield¹H NMR: (DMSO) δ (ppm): 7.79 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.00-6.95 (m, 2H), 6.74 (s, 2H), 4.32 (s, 2H), 3.80 (s, 6H), 3.73 (s, 3H).

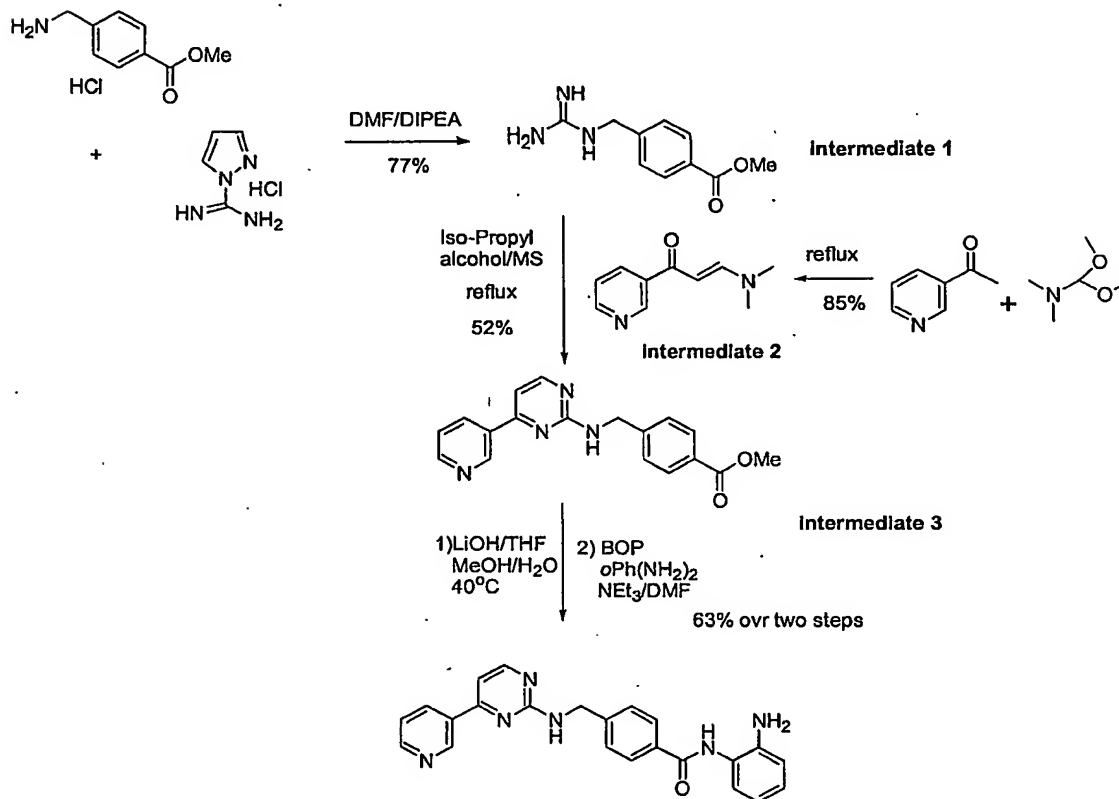
Examples 347-425

[0404] Examples 347 to 425 (compounds 492-570) were prepared using the same procedure as described for compound 44 to 491 in Example 40 to 346 (scheme 3 to 64).

Example 426

Synthesis of *N*-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide

Scheme 66



Step 1: Synthesis of 4-Guanidinomethyl-benzoic acid methyl ester

Intermediate 1

[0405] The mixture of 4-Aminomethyl-benzoic acid methyl ester HCl (15.7 g, 77.8 mmol) in DMF (85.6 mL) and DIPEA (29.5 mL, 171.2 mmol) was stirred at rt for 10 min. Pyrazole-1-carboxamidine HCl (12.55 g, 85.6 mmol) was added to the reaction mixture and then stirred at rt for 4 h to give clear solution. The reaction mixture was evaporated to dryness under vacuum. Saturated NaHCO₃ solution (35 mL) was added to give nice suspension. The suspension was filtered and the filter

cake was washed with cold water. The mother liquid was evaporated to dryness and then filtered. The two solids were combined and re-suspended over distilled H₂O (50 mL). The filter cake was then washed with minimum quantities of cold H₂O and ether to give 12.32 g white crystalline solid intermediate 1 (77% yield, M+1: 208 on MS).

Step 2: Synthesis of 3-Dimethylamino-1-pyridin-3-yl-propenone
Intermediate 2

[0406] 3-Acetyl-pyridine (30.0 g, 247.6 mmol) and DMF dimethyl acetal (65.8 mL, 495.2 mmol) were mixed together and then heated to reflux for 4h. The reaction mixture was evaporated to dryness and then 50 mL diethyl ether was added to give brown suspension. The suspension was filtered to give 36.97 g orange color crystalline product (85% yield, M+1: 177 on MS).

Step 3: Synthesis of 4-[(4-Pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzoic acid methyl ester Intermediate 3

[0407] Intermediate 1 (0.394 g, 1.9 mmol) and intermediate 2 (0.402 g, 2.3 mmol) and molecular sieves (0.2 g, 4A, powder, >5 micron) were mixed with isopropyl alcohol (3.8 mL). The reaction mixture was heated to reflux for 5h. MeOH (50 mL) was added and then heated to reflux. The cloudy solution was filtrated over a pad of celite. The mother liquid was evaporated to dryness and the residue was triturated with 3 mL EtOAc. The suspension was filtrated to give 0.317g white crystalline solid Intermediate 3 (52%, M+1: 321 on MS).

Step 4: Synthesis of N-(2-Amino-phenyl)-4-[(4-pyridin-3-yl-pyrimidin-2-ylamino)-methyl]-benzamide

[0408] Intermediate 3 (3.68 g, 11.5 mmol) was mixed with THF (23 mL), MeOH (23 mL) and H₂O (11.5 mL) at rt. LiOH (1.06 g, 25.3 mmol) was added to reaction mixture. The resulting reaction mixture was warmed up to 40°C overnight. HCl solution (12.8 mL, 2N) was added to adjust pH=3 when the mixture was cooled down to rt. The mixture was evaporated to dryness and then the solid was washed with minimum quantity of H₂O upon filtration. The filter cake was dried over freeze dryer to give 3.44 g acid of the title compound (95%, M+1: 307 on MS).

[0409] Acid (3.39g, 11.1 mmol) of the title compound, BOP (5.679g, 12.84 mmol) and o-Ph(NH₂)₂ (2.314 g, 21.4 mmol) were dissolved in the mixture of DMF (107 mL) and Et₃N (2.98 mL, 21.4 mmol). The reaction

mixture was stirred at rt for 5h and then evaporated to dryness. The residue was purified by flash column (pure EtOAc to 5% MeOH/EtOAc) and then interested fractions were concentrated. The final product was triturated with EtOAc to give 2.80 g of title product (66%, MS+1: 397 on MS). ^1H NMR (400 MHz, DMSO- D_6) δ (ppm): 9.57 (s, 1H), 9.22 (s, 1H), 8.66 (d, J = 3.5 Hz, 1H), 8.39 (d, J = 5.1 Hz, 2H), 8.00 (t, J = 6.5 Hz, 1H), 7.90 (d, J = 8.2 Hz, 2H), 7.50 (m, 3H), 7.25 (d, J = 5.1 Hz, 1H), 7.12 (d, J = 7.4 Hz, 1H), 6.94 (dd, J = 7.0, 7.8 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.57 (dd, J = 7.0, 7.8 Hz, 1H), 4.86 (s, 2H), 4.64 (d, J = 5.9 Hz, 2H).

Assay Example 1

Inhibition of Histone Deacetylase Enzymatic Activity

1. Human HDAC-1

[0410] HDAC inhibitors were screened against a cloned recombinant human HDAC-1 enzyme expressed and purified from a Baculovirus insect cell expression system. For deacetylase assays, 20,000 cpm of the [^3H]-metabolically labeled acetylated histone substrate (M. Yoshida et al., *J. Biol. Chem.* 265(28): 17174-17179 (1990)) was incubated with 30 μg of the cloned recombinant hHDAC-1 for 10 minutes at 37 $^\circ\text{C}$. The reaction was stopped by adding acetic acid (0.04 M, final concentration) and HCl (250 mM, final concentration). The mixture was extracted with ethyl acetate and the released [^3H]-acetic acid was quantified by scintillation counting. For inhibition studies, the enzyme was preincubated with compounds at 4 $^\circ\text{C}$ for 30 minutes prior to initiation of the enzymatic assay. IC_{50} values for HDAC enzyme inhibitors were determined by performing dose response curves with individual compounds and determining the concentration of inhibitor producing fifty percent of the maximal inhibition. IC_{50} values for representative compounds are presented in the third column of Table 5.

2. MTT Assay

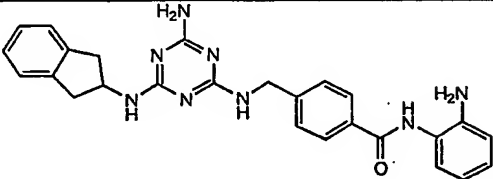
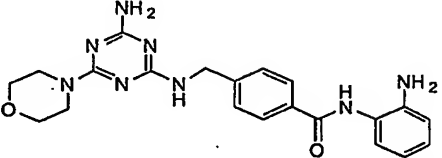
[0411] HCT116 cells (2000/well) were plated into 96-well tissue culture plates one day before compound treatment. Compounds at various concentrations were added to the cells. The cells were incubated for 72 hours at 37 $^\circ\text{C}$ in 5% CO_2 incubator. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide, Sigma) was added at a final concentration of 0.5 mg/ml and incubated with the cells for 4 hours before one volume of solubilization buffer (50% N,N-

dimethylformamide, 20% SDS, pH 4.7) was added onto the cultured cells. After overnight incubation, solubilized dye was quantified by colorimetric reading at 570 nM using a reference at 630 nM using an MR700 plate reader (Dynatech Laboratories Inc.). OD values were converted to cell numbers according to a standard growth curve of the relevant cell line. The concentration which reduces cell numbers to 50% of that of solvent treated cells is determined as MTT IC₅₀. IC₅₀ values for representative compounds are presented in the fourth column of Table 5.

3. Histone H4 acetylation in whole cells by immunoblots

[0412] T24 human bladder cancer cells growing in culture were incubated with HDAC inhibitors for 16 h. Histones were extracted from the cells after the culture period as described by M. Yoshida et al. (*J. Biol. Chem.* 265(28): 17174-17179 (1990)). 20 g of total histone protein was loaded onto SDS/PAGE and transferred to nitrocellulose membranes. Membranes were probed with polyclonal antibodies specific for acetylated histone H-4 (Upstate Biotech Inc.), followed by horse radish peroxidase conjugated secondary antibodies (Sigma). Enhanced Chemiluminescence (ECL) (Amersham) detection was performed using Kodak films (Eastman Kodak). Acetylated H-4 signal was quantified by densitometry. Representative data are presented in the fifth column of Table 5. Data are presented as the concentration effective for reducing the acetylated H-4 signal by 50% (EC₅₀).

Table 5a: Inhibition of Histone Deacetylase

| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|---|--------------------------------------|---------------------------------------|-------------------------------------|
| 8 |  | 0.4 | 0.5 | 1 |
| 9 |  | 2 | 0.7 | 5 |

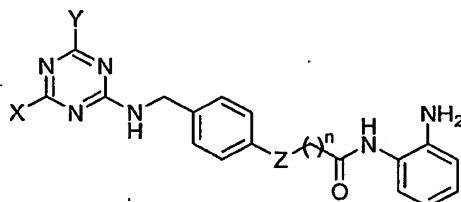
| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----------|--------------------------------------|---------------------------------------|-------------------------------------|
| 10 | | 2 | 0.6 | 1 |
| 11 | | 2 | 0.6 | 2 |
| 12 | | 2 | 2 | 5 |
| 14 | | 0.3 | 1 | 5 |
| 15 | | 0.5 | 0.2 | 3 |
| 16 | | 1 | 0.4 | 1 |
| 17 | | 0.9 | 1 | 2 |
| 18 | | 0.8 | 0.6 | 3 |
| 18b | | 0.6 | 5 | 10 |

| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----------|--------------------------------------|---------------------------------------|-------------------------------------|
| 19 | | 0.9 | 1 | 1 |
| 20 | | 0.5 | 0.3 | 1 |
| 21 | | 4 | 4 | 25 |
| 22 | | 3 | 0.8 | 1 |
| 23 | | 2 | 0.7 | 1 |
| 24 | | 3 | 0.6 | 1 |
| 25 | | 0.8 | 0.3 | 5 |
| 26 | | 0.5 | 2 | na |
| 27 | | 0.4 | 2 | na |

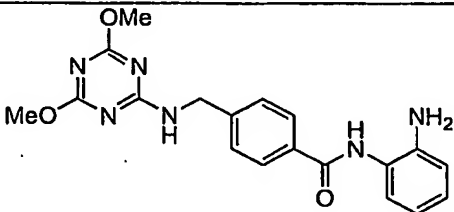
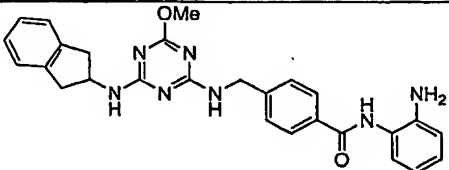
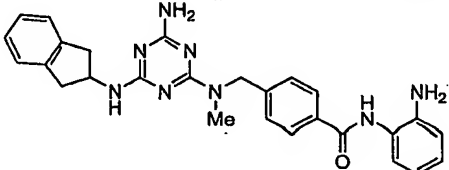
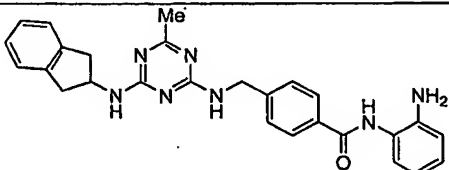
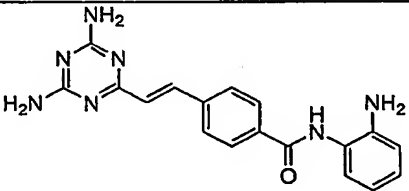
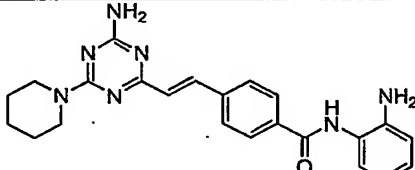
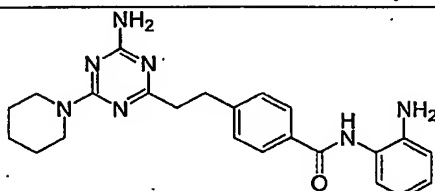
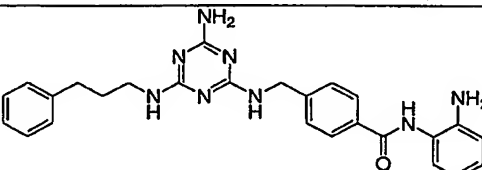
| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----------|--------------------------------------|---------------------------------------|-------------------------------------|
| 28 | | 2 | 0.5 | 1 |
| 29 | | 2 | 2 | 1 |
| 30 | | 1 | 3 | 1 |
| 83 | | 3 | 5 | 5 |

(na = not available; 99 = >25 μM)

Table 5b



| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT(HCT116) IC ₅₀ (μM) | H4Ac(T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|--------------------------------------|------------------------------------|
| 135 | 204 | | 4 | na | 5 |
| 136 | 207 | | 0.4 | 0.6 | 2 |
| 137 | 210 | | 3 | 0.9 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT(HCT116) IC ₅₀ (μM) | H4Ac(T24) EC ₅₀ (μM) |
|------|-----|---|---------------------------------------|--------------------------------------|------------------------------------|
| 138 | 212 |  | 3 | 1 | 1 |
| 139 | 214 |  | 3 | 0.9 | 1 |
| 140 | 216 |  | 0.5 | 0.4 | 2 |
| 141 | 218 |  | 0.1 | 0.5 | na |
| 142 | 220 |  | 7 | 6 | na |
| 143a | 223 |  | 11 | 2 | na |
| 143b | 224 |  | 5 | 3 | na |
| 329 | 470 |  | 2 | 0.7 | 3 |

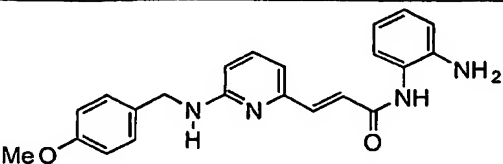
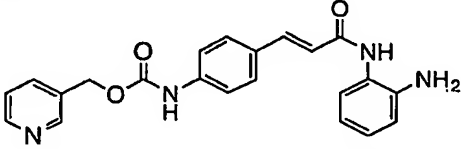
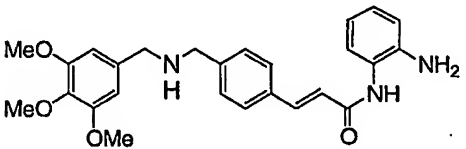
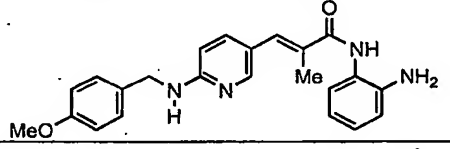
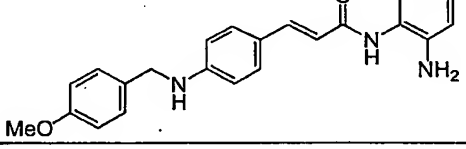
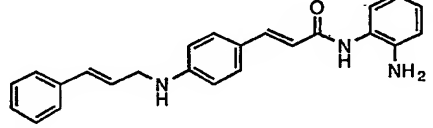
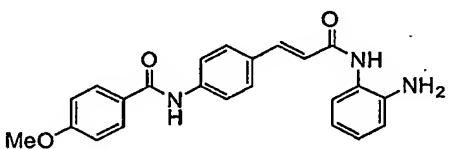
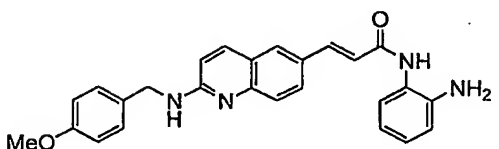
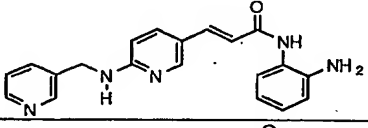
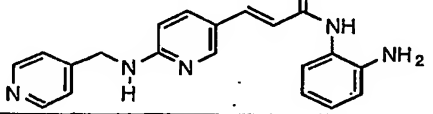
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μ M) | MTT(HCT116) IC ₅₀ (μ M) | H4Ac(T24) EC ₅₀ (μ M) |
|-----|-----|-----------|---|--|--|
| 330 | 471 | | 0.4 | 1 | 3 |
| 331 | 472 | | 3 | 1 | 1 |
| 332 | 473 | | 4 | 3 | na |
| 333 | 474 | | 3 | 1 | 1 |
| 334 | 475 | | 0.6 | 2 | na |
| 335 | 476 | | 2 | 1 | 2 |
| 336 | 477 | | 1 | 0.7 | na |
| 337 | 478 | | 3 | 0.7 | na |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μ M) | MTT(HCT116) IC ₅₀ (μ M) | H4Ac(T24) EC ₅₀ (μ M) |
|-----|-----|-----------|---|--|--|
| 338 | 479 | | 0.4 | 0.6 | na |
| 339 | 480 | | 0.8 | 0.5 | na |
| 340 | 481 | | 6 | 0.7 | na |
| 341 | 482 | | 0.1 | 0.7 | na |
| 342 | 483 | | 4 | na | na |
| 343 | 484 | | 2 | 0.3 | na |
| 344 | 485 | | 0.4 | 3 | na |

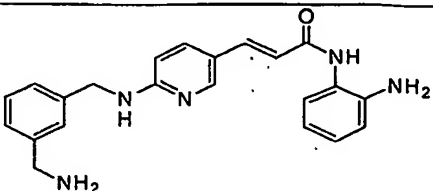
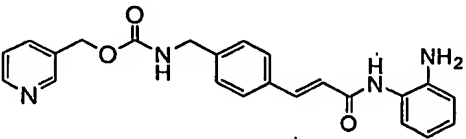
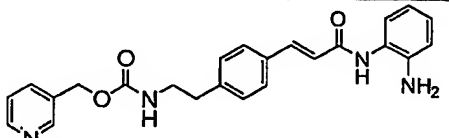
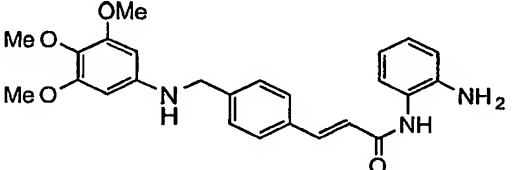
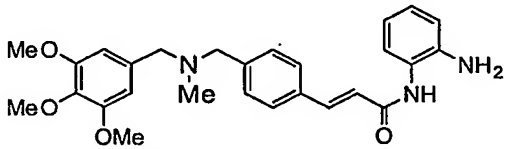
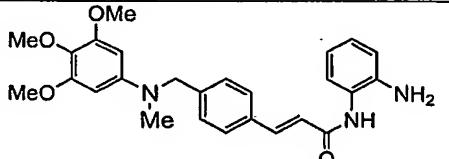
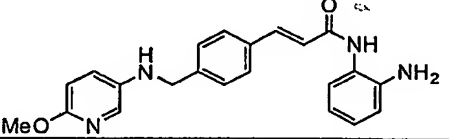
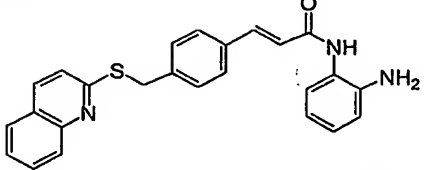
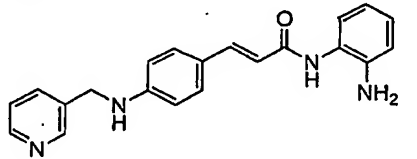
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Table 5c

| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μ M) | MTT(HCT116) IC ₅₀ (μ M) | H4Ac(T24) EC ₅₀ (μ M) |
|-----|-----------|--|--|--|
|-----|-----------|--|--|--|

| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μM) | MTT(HCT116) IC ₅₀ (μM) | H4Ac(T24) EC ₅₀ (μM) |
|-----|---|--------------------------------------|--------------------------------------|------------------------------------|
| 51 |  | 22 | 4 | na |
| 55b |  | 3 | 8 | 3 |
| 59 |  | 12 | 22 | na |
| 61b |  | 7 | 12 | na |
| 65 |  | 4 | 37 | na |
| 71 |  | 10 | 44 | na |
| 72 |  | 16 | 21 | na |
| 88 |  | na | >39 | na |
| 90 |  | 10 | 5 | 5 |
| 91 |  | 4 | 7 | 5 |

| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μ M) | MTT(HCT116) IC ₅₀ (μ M) | H4Ac(T24) EC ₅₀ (μ M) |
|-----|-----------|--|--|--|
| 92 | | 5 | 2 | 3 |
| 93 | | 3 | 1 | 5 |
| 94 | | 3 | 2 | 5 |
| 95 | | 3 | 2 | 10 |
| 96 | | 4 | 3 | 25 |
| 97 | | 10 | 12 | na |
| 98 | | 0.4 | 2 | 15 |
| 99 | | 2 | 5 | 10 |
| 100 | | 4 | 3 | 5 |
| 101 | | 3 | 0.9 | 5 |

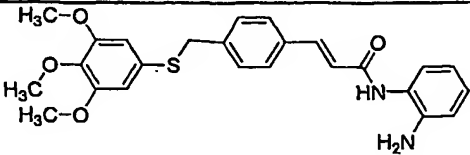
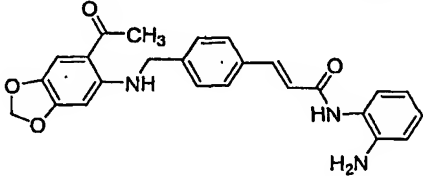
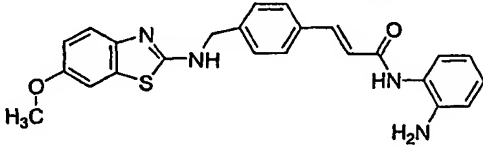
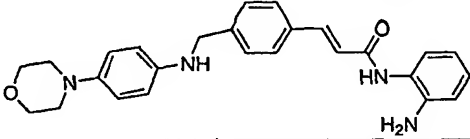
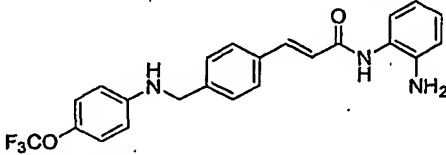
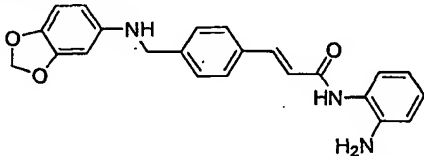
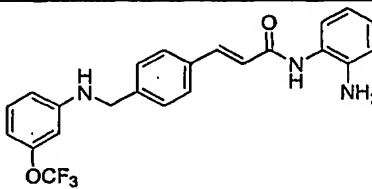
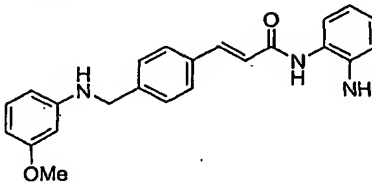
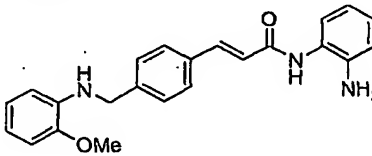
| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μM) | MTT(HCT116) IC ₅₀ (μM) | H4Ac(T24) EC ₅₀ (μM) |
|-----|---|--------------------------------------|--------------------------------------|------------------------------------|
| 102 |  | 20 | 6 | na |
| 104 |  | 10 | 9 | 5 |
| 105 |  | 16 | 14 | na |
| 106 |  | 2 | 2 | 1 |
| 107 |  | 15 | 17 | na |
| 108 |  | 3 | 5 | 5 |
| 109 |  | 5 | 8 | 15 |
| 110 |  | 3 | 999 | na |
| 111 |  | 10 | 2 | 99 |

| Cpd | Structure | HumanHDAC-1 IC ₅₀ (μ M) | MTT(HCT116) IC ₅₀ (μ M) | H4Ac(T24) EC ₅₀ (μ M) |
|-----|-----------|--|--|--|
| 112 | | 2 | 5 | 5 |
| 113 | | | 0.3 | 5 |
| 114 | | 25 | 0.5 | 99 |
| 115 | | 15 | 9 | na |
| 116 | | 4 | 2 | 5 |
| 117 | | 7 | 3 | na |
| 118 | | 11 | 8 | na |

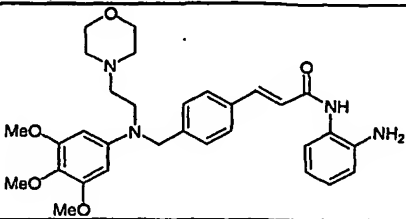
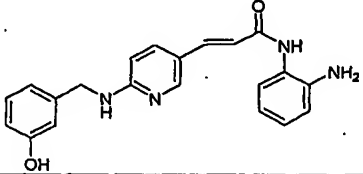
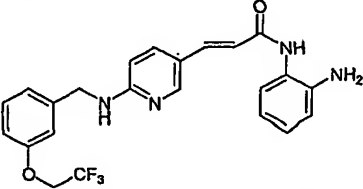
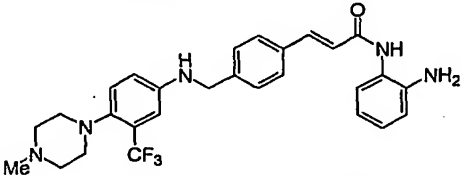
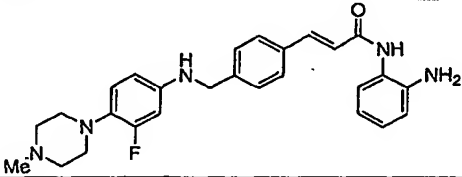
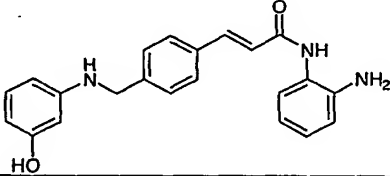
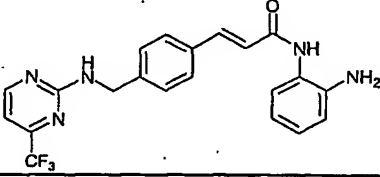
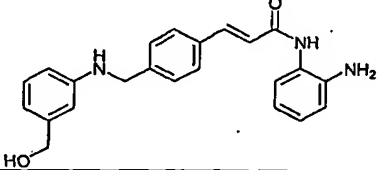
Table 5d

| Ex. | Cpd | Structure | HDAC-1 IC ₅₀ (μ M) | MTT (HCT116) IC ₅₀ (μ M) | H4Ac (T24) EC ₅₀ (μ M) |
|-----|-----|-----------|---------------------------------------|---|---|
| 338 | 481 | | 22 | 10 | - |
| 339 | 484 | | 20 | 12 | - |

| Ex. | Cpd | Structure | HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------|---------------------------------------|-------------------------------------|
| 347 | 492 | | 4 | 9 | 10 |
| 348 | 493 | | 4 | 5 | - |
| 349 | 494 | | 3 | 4 | - |
| 350 | 495 | | 4 | 7 | - |
| 351 | 496 | | 8 | 13 | - |
| 352 | 497 | | 15 | 6 | - |
| 353 | 498 | | >25 | - | - |
| 354 | 499 | | >25 | 2 | >25 |

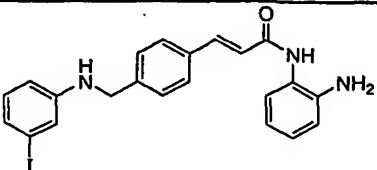
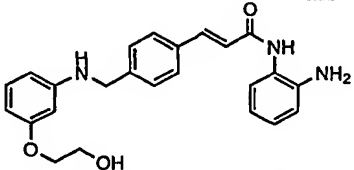
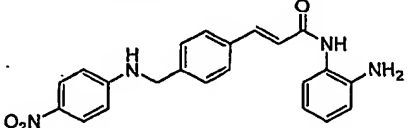
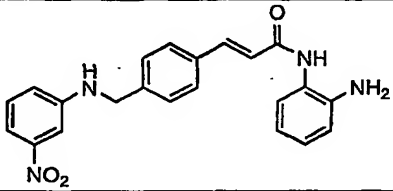
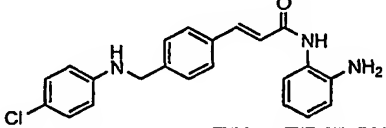
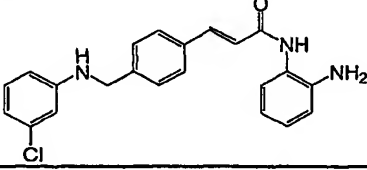
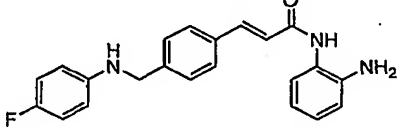
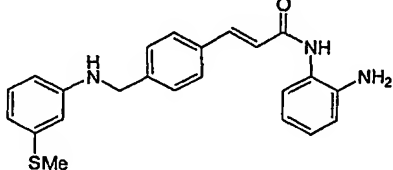
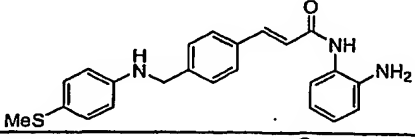
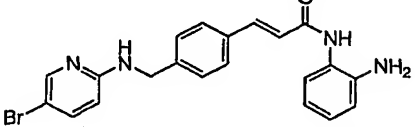
| Ex. | Cpd | Structure | HDAC-1 IC50 (μM) | MTT (HCT116) IC50 (μM) | H4Ac (T24) EC50 (μM) |
|-----|-----|---|---------------------|---------------------------|-------------------------|
| 355 | 500 |  | 23 | 37 | - |
| 356 | 501 |  | 4 | 10 | - |
| 357 | 502 |  | 3 | >25 | - |
| 358 | 503 |  | 5 | >25 | - |
| 359 | 504 |  | 5 | >25 | - |
| 360 | 505 |  | 3 | 6 | - |
| 361 | 506 |  | 15 | 11 | - |
| 362 | 507 |  | 17 | 10 | - |
| 363 | 508 |  | 22 | 11 | - |

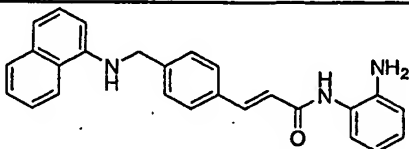
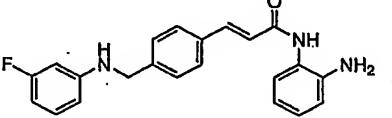
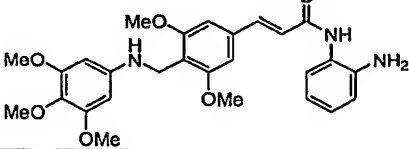
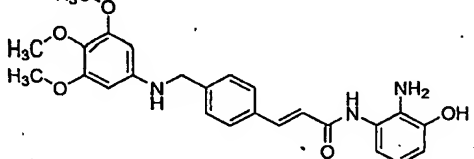
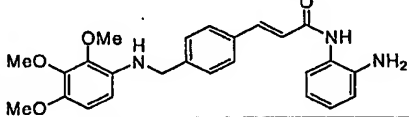
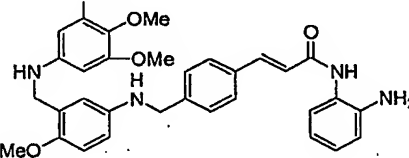
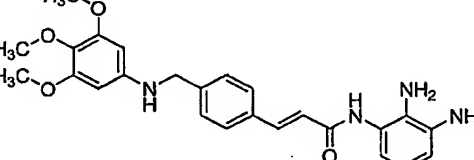
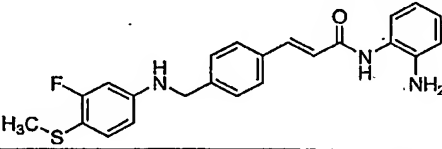
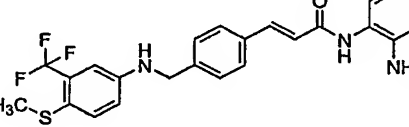
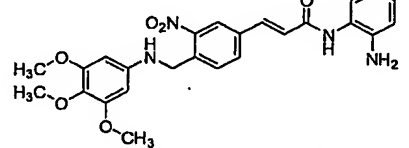
| Ex. | Cpd | Structure | HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------|---------------------------------------|-------------------------------------|
| 364 | 509 | | 17 | 11 | - |
| 365 | 510 | | 6 | 5 | - |
| 366 | 511 | | 4 | >25 | - |
| 367 | 512 | | 3 | 3 | 5 |
| 371 | 516 | | 15 | 15 | - |
| 372 | 517 | | 6 | 5 | - |
| 373 | 518 | | 4 | 2 | 5 |
| 374 | 519 | | 99 | 6 | - |
| 375 | 520 | | 5 | 3 | - |
| 376 | 521 | | 5 | 2 | 10 |
| 377 | 522 | | 17 | 30 | - |

| Ex. | Cpd | Structure | HDAC-1 IC50 (μM) | MTT (HCT116) IC50 (μM) | H4Ac (T24) EC50 (μM) |
|-----|-----|---|---------------------|---------------------------|-------------------------|
| 378 | 523 |  | 8 | 6 | 10 |
| 379 | 524 |  | 3 | 2 | 3 |
| 380 | 525 |  | 3 | 4 | 5 |
| 381 | 526 |  | 2 | 0.8 | 1 |
| 382 | 527 |  | 4 | 3 | - |
| 383 | 528 |  | 20 | 32 | - |
| 384 | 529 |  | 5 | 17 | - |
| 385 | 530 |  | 8 | 9 | - |

| Ex. | Cpd | Structure | HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------|---------------------------------------|-------------------------------------|
| 386 | 531 | | 3 | 2 | 20 |
| 387 | 532 | | 3 | 5 | - |
| 388 | 533 | | 5 | 11 | - |
| 389 | 534 | | 3 | 5 | - |
| 390 | 535 | | 4 | 6 | - |
| 391 | 536 | | 18 | 9 | - |
| 392 | 537 | | 11 | 2 | >25 |
| 393 | 538 | | 4 | 12 | - |

| Ex. | Cpd | Structure | HDAC-1 IC50 (μM) | MTT (HCT116) IC50 (μM) | H4Ac (T24) EC50 (μM) |
|-----|-----|-----------|---------------------|---------------------------|-------------------------|
| 394 | 539 | | 2 | 10 | - |
| 395 | 540 | | 10 | 10 | - |
| 396 | 541 | | 4 | 12 | - |
| 397 | 542 | | 2 | 5 | 4 |
| 398 | 543 | | 15 | >25 | - |
| 399 | 544 | | 17 | 45 | - |
| 400 | 545 | | 2 | 12 | - |
| 401 | 546 | | 3 | 10 | - |
| 402 | 547 | | 4 | 8 | - |

| Ex. | Cpd | Structure | HDAC-1 IC50 (μ M) | MTT (HCT116) IC50 (μ M) | H4Ac (T24) EC50 (μ M) |
|-----|-----|---|---------------------------|---------------------------------|-------------------------------|
| 403 | 548 |  | 3 | 9 | - |
| 404 | 549 |  | 4 | 19 | - |
| 405 | 550 |  | 4 | 15 | - |
| 406 | 551 |  | 24 | 9 | - |
| 407 | 552 |  | 4 | 22 | - |
| 408 | 553 |  | 4 | 12 | - |
| 409 | 554 |  | 15 | 12 | - |
| 410 | 555 |  | 14 | 7 | - |
| 411 | 556 |  | 1 | 0.4 | 15 |
| 412 | 557 |  | 4 | 6 | - |

| Ex. | Cpd. | Structure | HDAC-1 IC50 (μM) | MTT (HCT116) IC50 (μM) | H4Ac (T24) EC50 (μM) |
|-----|------|---|---------------------|---------------------------|-------------------------|
| 413 | 558 |  | 7 | 10 | - |
| 414 | 559 |  | 4 | 11 | - |
| 415 | 560 |  | 21 | 6 | - |
| 416 | 561 |  | >25 | >25 | - |
| 417 | 562 |  | 5 | 5 | - |
| 418 | 563 |  | 24 | 6 | - |
| 419 | 564 |  | >25 | >25 | - |
| 420 | 565 |  | 5 | 17 | - |
| 421 | 566 |  | 3 | 16 | - |
| 422 | 567 |  | 13 | 3 | - |

| Ex. | Cpd | Structure | HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------|---------------------------------------|-------------------------------------|
| 423 | 568 | | >25 | 39 | - |
| 424 | 569 | | 18 | 6 | - |
| 425 | 570 | | 6 | 0.6 | 2 |

Table 5e

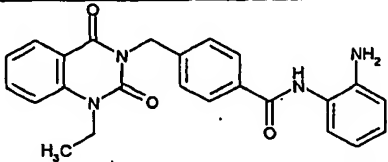
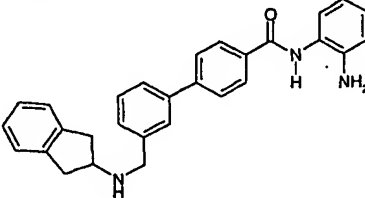
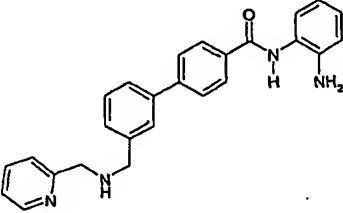
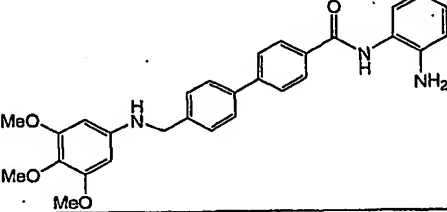
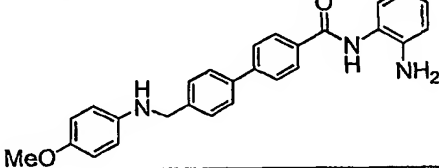
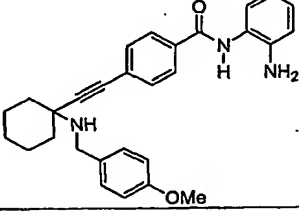
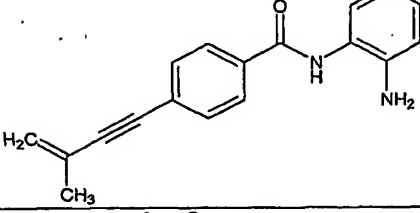
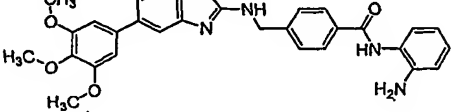
| Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 87 | | 2 | 1 | 5 |
| 126 | | 0.3 | 0.2 | 1 |
| 128 | | 1 | 0.3 | 5 |
| 131 | | 0.3 | 0.9 | 2 |
| 139 | | 3 | 3 | 5 |
| 141 | | 7 | 10 | na |

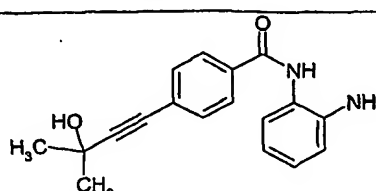
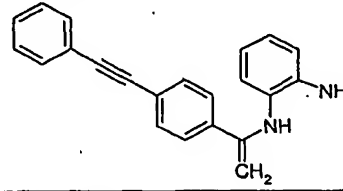
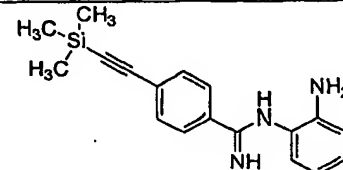
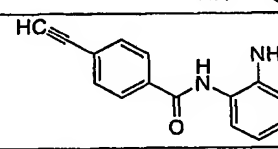
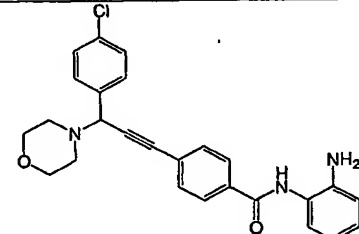
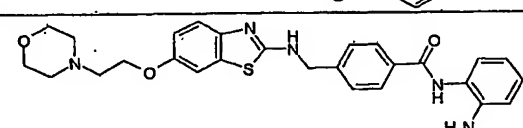
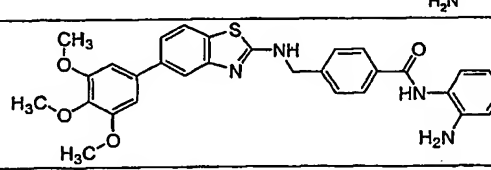
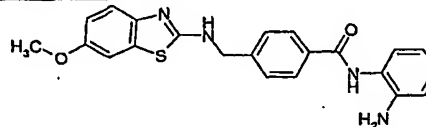
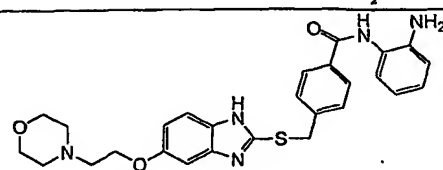
| Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 149 | | 1 | 5 | 5 |
| 152 | | 0.3 | 11 | na |
| 154 | | 0.3 | 0.4 | <1 |
| 155 | | 0.4 | 0.4 | 1 |
| 157 | | 2 | 0.6 | 1 |
| 158 | | 0.4 | 0.2 | 1 |
| 164 | | 3 | 2 | 3 |
| 165 | | 9 | 4 | 25 |
| 166 | | 2 | 5 | 5 |
| 167 | | 4 | 0.5 | 2 |
| 168 | | 3 | 0.8 | 2 |

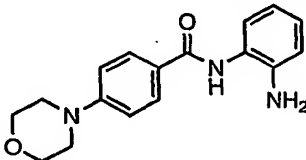
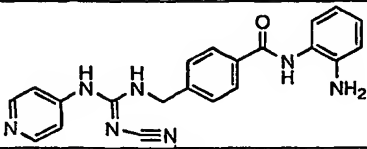
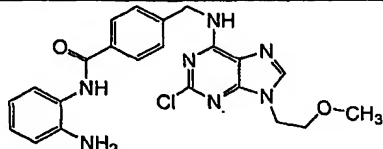
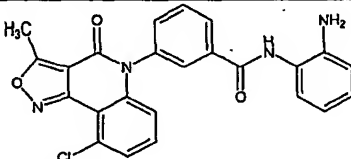
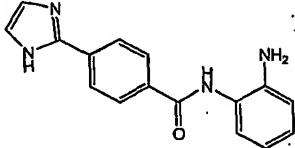
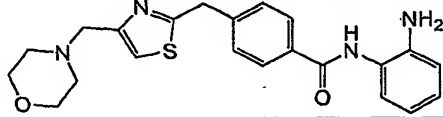
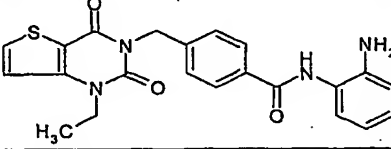
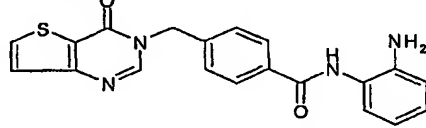
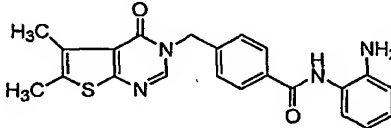
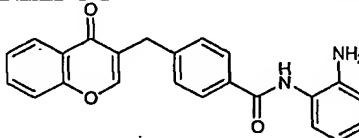
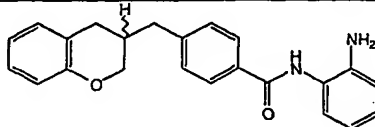
| Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 169 | | 0.3 | 0.7 | 1 |
| 171 | | 8 | 3 | 25 |
| 172 | | 0.4 | 1 | 3 |
| 174 | | 4 | 0.4 | 5 |
| 175 | | 4 | 0.5 | 3 |
| 176 | | 5 | 1 | 3 |
| 177 | | 1 | 0.4 | 1 |

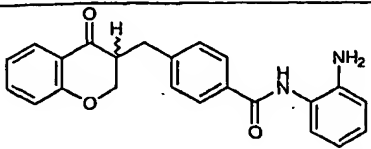
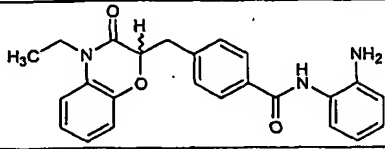
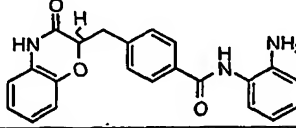
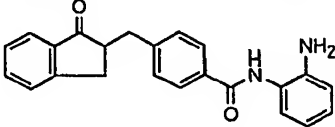
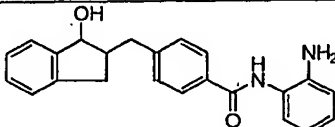
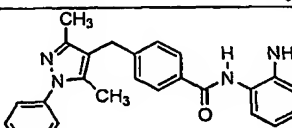
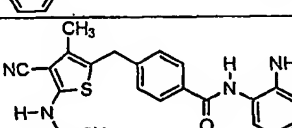
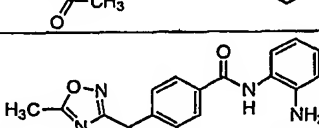
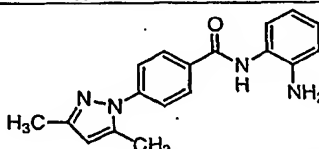
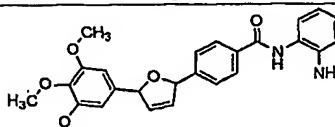
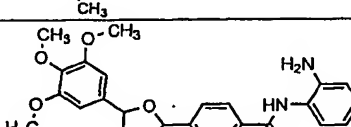
Table 5f

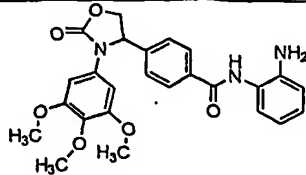
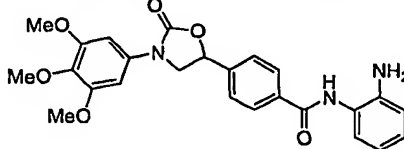
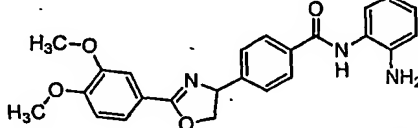
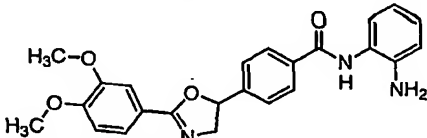
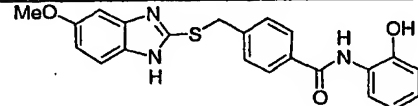
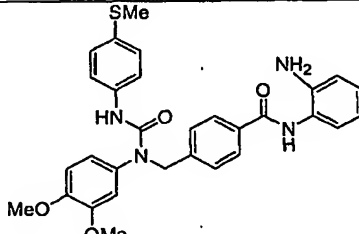
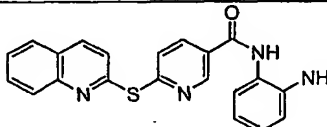
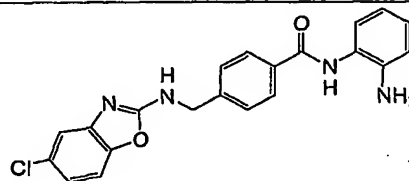
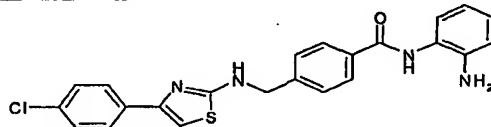
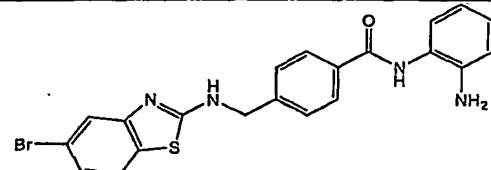
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|--------------------------------------|
| 117 | 179 | | 1 | 0.3 | 1 |
| 118 | 180 | | 3 | 2 | 5 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 119 | 181 |  | 0.5 | 0.4 | 1 |
| 122 | 186 |  | 2 | 2 | 2 |
| 123 | 187 |  | 2 | 5 | 2 |
| 125 | 189 |  | 3 | 2 | 5 |
| 126 | 190 |  | 3 | 1 | >5 |
| 127 | 192 |  | 2 | 1 | 3 |
| 128 | 193 |  | 4 | 16 | |
| 129 | 194 |  | 3 | 11 | |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 130 | 195 |  | 7 | 9 | |
| 131 | 196 |  | 4 | 3 | |
| 132 | 198 |  | 24 | 14 | |
| 133 | 199 |  | 7 | 9 | |
| 134 | 201 |  | 11 | 5 | |
| 144 | 228 |  | 3 | 0.3 | 1 |
| 145 | 231 |  | 4 | 1 | 3 |
| 146 | 233 |  | 0.9 | 0.3 | 1 |
| 147 | 236 |  | 5 | 6 | |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 148 | 238 |  | 3 | 6 | |
| 149 | 240 |  | 1.8 | 10 | |
| 150 | 243 |  | 2 | 0.8 | 1 |
| 151 | 247 |  | 3 | 0.6 | 2 |
| 152 | 249 |  | 4 | 1 | 2 |
| 153 | 252 |  | 8 | 1 | 2 |
| 154 | 255 |  | 2 | 0.8 | 1 |
| 155 | 257 |  | 0.4 | 0.4 | 1 |
| 156 | 259 |  | 3 | 0.3 | 1 |
| 157 | 262 |  | 0.5 | 0.3 | 1 |
| 158 | 265 |  | 2 | 2 | 3 |

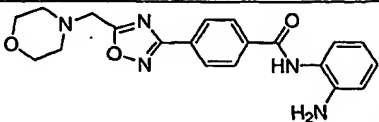
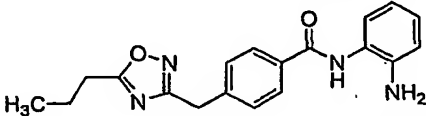
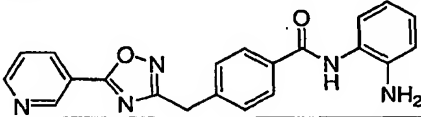
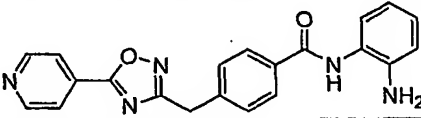
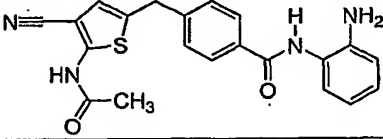
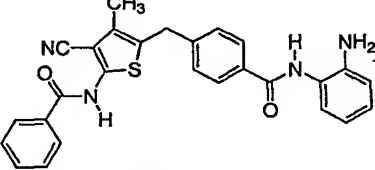
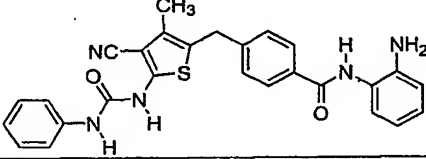
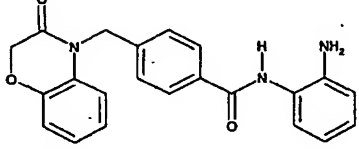
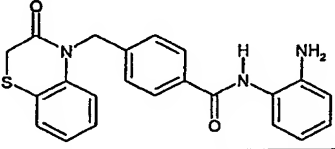
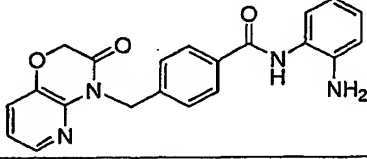
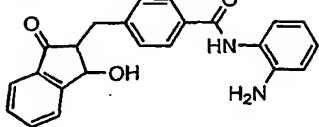
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 159 | 266 |  | 0.4 | 0.9 | 2 |
| 160 | 269 |  | 9 | 4 | |
| 161 | 270 |  | 4 | 1 | 5 |
| 162 | 272 |  | 2 | 0.6 | <1 |
| 163 | 275 |  | 4 | 0.9 | 2 |
| 164 | 277 |  | 4 | 0.3 | 1 |
| 165 | 281 |  | 0.5 | 0.6 | 1 |
| 166 | 284 |  | 3 | 5 | |
| 167 | 286 |  | 5 | 2 | |
| 168 | 289 |  | 17 | 5 | |
| 169 | 290 |  | 11 | 3 | |

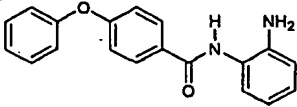
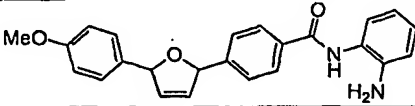
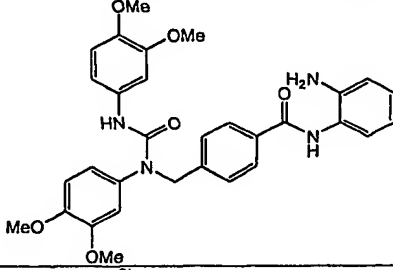
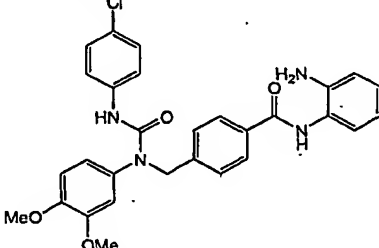
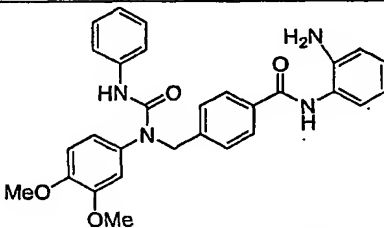
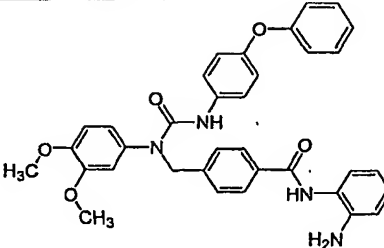
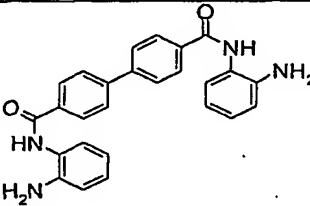
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 170 | 296 |  | 20 | 7 | |
| 171 | 297 |  | 7 | 0.4 | 1 |
| 172 | 301 |  | 3 | 3 | |
| 173 | 305 |  | 4 | 2 | |
| 174 | 311 |  | 0.9 | 0.7 | 1 |
| 178 | 317 |  | 2 | 0.3 | 1 |
| 179 | 319 |  | 4 | 8 | |
| 180 | 320 |  | 2 | | 1 |
| 181 | 321 |  | 0.5 | 0.3 | 5 |
| 182 | 322 |  | 0.7 | 0.4 | 2 |

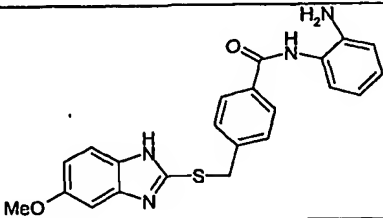
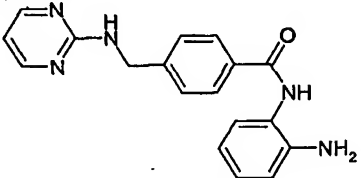
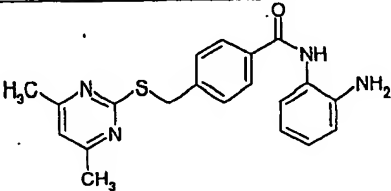
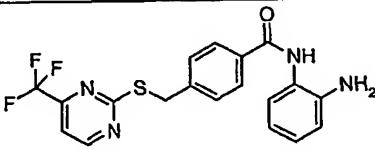
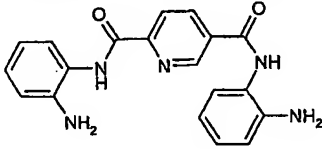
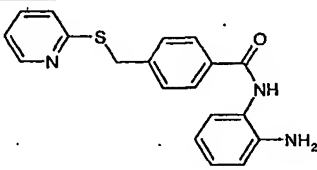
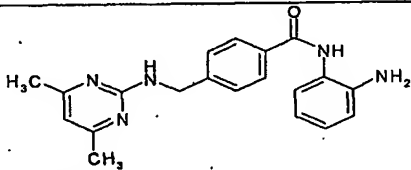
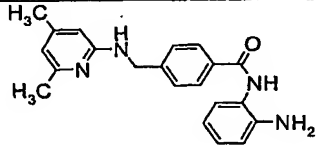
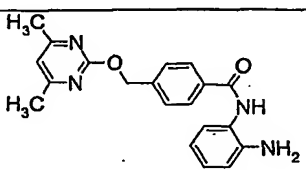
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 183 | 323 | | 1 | 0.6 | 1 |
| 184 | 325 | | 0.3 | 1 | 2 |
| 185 | 326 | | 1 | 1 | 3 |
| 186 | 327 | | 2 | 5 | 3 |
| 187 | 328 | | 17 | 10 | |
| 189 | 330 | | 3 | 2 | 1 |
| 190 | 331 | | 4 | 10 | |
| 191 | 332 | | 0.4 | 1 | 5 |
| 192 | 333 | | 2 | 0.1 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 193 | 334 | | 8 | 0.2 | 1 |
| 195 | 336 | | 1 | 0.4 | <1 |
| 196 | 337 | | 3 | 0.6 | 1 |
| 197 | 338 | | 2 | 0.5 | 3 |
| 198 | 339 | | 4 | 3 | |
| 199 | 340 | | 2 | 1 | 1 |
| 200 | 341 | | 4 | 1 | 3 |
| 201 | 342 | | 3 | 0.4 | 1 |
| 202 | 343 | | 0.5 | 0.3 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 203 | 344 | | 0.5 | 0.2 | 1 |
| 204 | 345 | | 0.4 | 0.8 | 1 |
| 205 | 346 | | 3 | 0.5 | <1 |
| 206 | 347 | | 2 | 0.6 | 2 |
| 207 | 348 | | 2 | 0.3 | 1 |
| 208 | 349 | | 13 | 1 | 3 |
| 209 | 350 | | 2 | 1 | 5 |
| 211 | 352 | | 16 | 9 | |
| 212 | 353 | | 3 | 10 | |
| 213 | 354 | | 15 | 5 | |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 214 | 355 |  | 25 | 10 | |
| 215 | 356 |  | 5 | 2 | |
| 216 | 357 |  | 4 | 0.4 | 2 |
| 217 | 358 |  | 3 | 1 | 2 |
| 218 | 359 |  | 2 | 0.3 | 1 |
| 219 | 360 |  | 5 | 0.2 | 1 |
| 220 | 361 |  | 2 | 0.5 | 1 |
| 221 | 362 |  | 2 | 0.7 | 1 |
| 222 | 363 |  | 1 | 0.3 | 3 |
| 223 | 364 |  | 4 | 0.6 | |
| 224 | 365 |  | 3 | 0.6 | 3 |

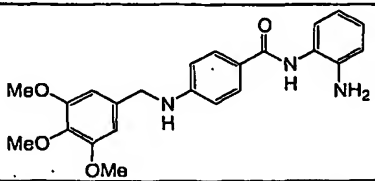
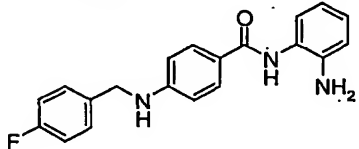
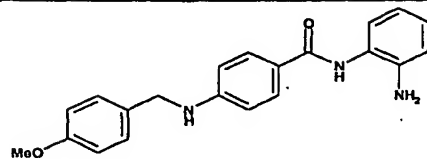
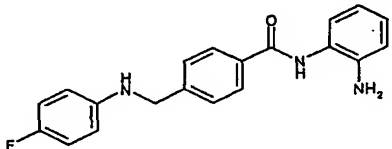
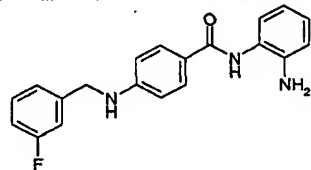
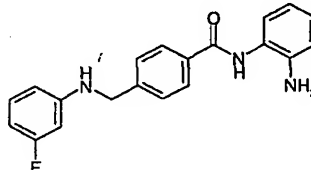
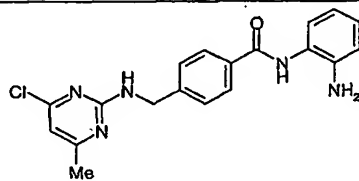
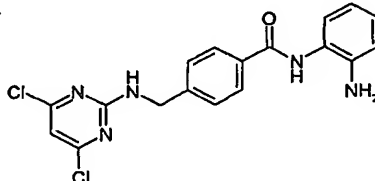
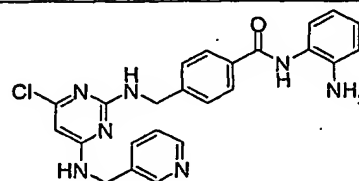
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 225 | 366 |  | 14 | 10 | |
| 226 | 367 |  | 6 | 2 | 5 |
| 230 | 371 |  | 4 | 0.5 | 2 |
| 231 | 372 |  | 2 | 0.2 | 1 |
| 232 | 373 |  | 4 | 0.4 | 1 |
| 233 | 374 |  | 2.5 | 0.3 | 1 |
| 234 | 375 |  | 3 | 4 | 25 |

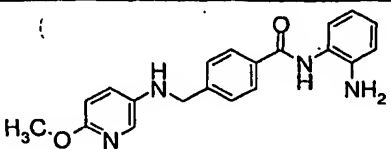
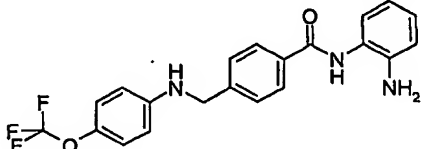
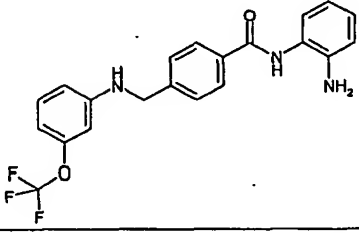
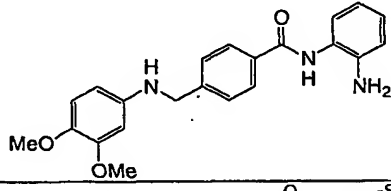
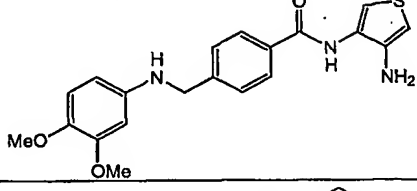
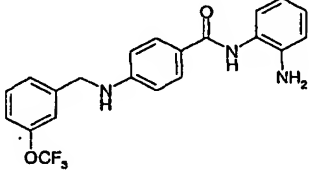
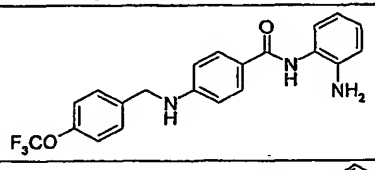
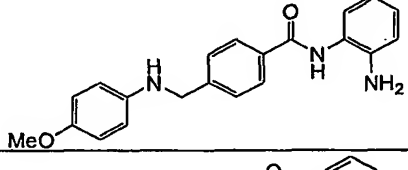
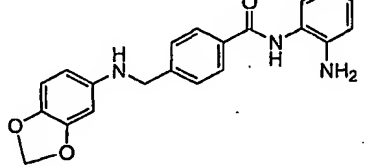
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 235 | 376 |  | 3 | 0.1 | 1 |
| 236 | 377 |  | 4 | 2 | 3 |
| 237 | 378 |  | 2 | 0.7 | 2 |
| 238 | 379 |  | 2 | 0.6 | 15 |
| 239 | 380 |  | 6 | 8 | |
| 240 | 381 |  | 2 | 1 | 2 |
| 241 | 382 |  | 3 | 1 | 3 |
| 242 | 383 |  | 2 | 0.5 | 2 |
| 243 | 384 |  | 3 | 2 | 5 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 244 | 385 | | 3 | 1 | 2 |
| 245 | 386 | | 3 | 1 | 1 |
| 246 | 387 | | 2 | 1 | 1 |
| 247 | 388 | | 3 | 0.4 | 5 |
| 248 | 389 | | 3 | 0.2 | 1 |
| 249 | 390 | | 2 | 0.8 | 5 |
| 250 | 391 | | 1 | 0.9 | 3 |
| 251 | 392 | | 4 | 1 | 1 |
| 252 | 393 | | 4 | 0.6 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 253 | 394 | | 4 | 2 | 25 |
| 254 | 395 | | 2 | 1 | 5 |
| 255 | 396 | | 2 | 0.7 | 5 |
| 256 | 397 | | 1 | 0.6 | 4 |
| 258 | 399 | | 14 | 9 | |
| 259 | 400 | | 8 | 0.3 | 2 |
| 260 | 401 | | 6 | 0.3 | 2 |
| 261 | 402 | | 14 | 0.4 | 1 |
| 262 | 403 | | 1 | 0.2 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 263 | 404 | | 3 | 0.6 | 5 |
| 264 | 405 | | 5 | 1 | 5 |
| 265 | 406 | | 3 | 11 | |
| 266 | 407 | | 3 | 2 | |
| 267 | 408 | | 4 | 2 | |
| 268 | 409 | | 3 | 1 | 9999 |
| 269 | 410 | | 0.9 | 0.1 | >5 |
| 270 | 411 | | 2 | | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 271 | 412 |  | 3 | 2 | 3 |
| 272 | 413 |  | 2 | 2 | 3 |
| 273 | 414 |  | 3 | 1 | 1 |
| 274 | 415 |  | 3 | 1 | 3 |
| 275 | 416 |  | 3 | 0.6 | 1 |
| 276 | 417 |  | 3 | 1 | 1 |
| 277 | 418 |  | 3 | 0.9 | 2 |
| 278 | 419 |  | 2 | 1 | 5 |
| 279 | 420 |  | 3 | 0.7 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|------|------|---|---------------------------------------|---------------------------------------|---|
| 280 | 421 |  | 4 | 0.6 | 1 |
| 281 | 422 |  | <0.05 | 0.9 | 5 |
| 282 | 423 |  | 0.5 | 1 | 3 |
| 283a | 424b |  | 2 | 0.4 | 1 |
| 283b | 424c |  | 3 | 0.8 | 3 |
| 284 | 425 |  | 2 | 0.6 | 5 |
| 285 | 426 |  | 2 | 1 | 10 |
| 286 | 427 |  | 0.6 | 2 | 1 |
| 287 | 428 |  | 0.7 | 0.7 | 1 |

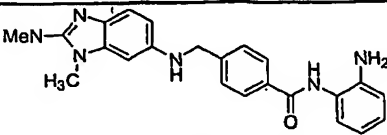
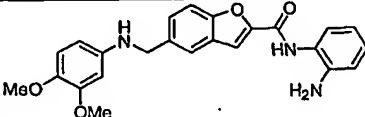
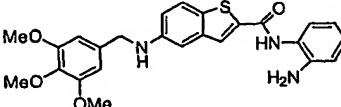
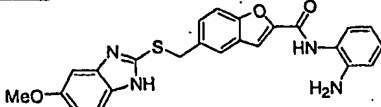
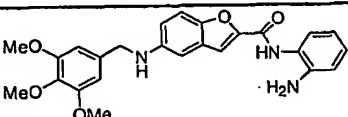
| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 288 | 429 | | 4 | 0.9 | 1 |
| 289 | 430 | | 5 | 0.7 | 1 |
| 290 | 431 | | 5 | 5 | |
| 291 | 432 | | 2 | 1 | 3 |
| 292 | 432 | | 2 | 0.6 | 1 |
| 293 | 434 | | 4 | 0.6 | 2 |
| 294 | 435 | | 3 | 0.6 | 1 |
| 295 | 436 | | 5 | 0.8 | 5 |
| 296 | 437 | | 3 | 0.4 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 297 | 438 | | 5 | 0.6 | 1 |
| 298 | 439 | | 3 | 0.4 | 1 |
| 299 | 440 | | 4 | 0.1 | 2 |
| 300 | 441 | | 2 | 0.8 | 2 |
| 301 | 442 | | 17 | 0.4 | 1 |
| 302 | 443 | | | | |
| 303 | 444 | | | | |
| 304 | 445 | | 16 | 6 | |
| 305 | 446 | | 21 | 7 | |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 307 | 448 | | 3 | 0.2 | 2 |
| 308 | 449 | | 1 | 6 | |
| 309 | 450 | | 3 | 2 | |
| 310 | 451 | | 4 | 0.2 | 3 |
| 311 | 452 | | 3 | 0.3 | 2 |
| 312 | 453 | | 9999 | 37 | |
| 313 | 454 | | 4 | 2 | 5 |
| 314 | 455 | | 4 | 0.7 | 1 |
| 315 | 456 | | 3 | 0.4 | 8888 |
| 316 | 457 | | 9999 | 9999 | |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 317 | 458 | | 3 | 0.3 | 2 |
| 318 | 459 | | 4 | 0.3 | 1 |
| 319 | 460 | | 3 | 1 | 1 |
| 320 | 461 | | 1.4 | 0.3 | 1 |
| 321 | 462 | | 4 | 0.3 | 1 |
| 322 | 463 | | 12 | 6 | |
| 323 | 464 | | 4 | 11 | |
| 324 | 465 | | 2 | 9999 | 9999 |
| 325 | 466 | | 3 | 2 | 1 |
| 326 | 467 | | 4 | 0.4 | 2 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|-----------|---------------------------------------|---------------------------------------|---|
| 327 | 468 | | 2 | 8 | <1 |
| 426 | 571 | | 4 | 11 | |
| 427 | 572 | | 1.5 | 5 | 5 |
| 428 | 573 | | 7 | 0.4 | 1 |
| 429 | 574 | | 13 | 0.7 | 3 |
| 430 | 575 | | 2 | 0.2 | 1 |
| 431 | 576 | | 5 | 6 | |
| 432 | 577 | | 2 | 0.5 | 2 |
| 433 | 578 | | 0.6 | 0.1 | 1 |
| 434 | 579 | | 2 | 0.5 | 1 |

| Ex | Cpd | Structure | Human HDAC-1 IC ₅₀ (μM) | MTT (HCT116) IC ₅₀ (μM) | H4 Ac (T24) EC ₅₀ (μM) |
|-----|-----|---|---------------------------------------|---------------------------------------|---|
| 435 | 580 |  | 4 | 0.3 | <1 |
| 436 | 587 |  | 5 | 0.8 | 2 |
| 437 | 590 |  | 2 | 2 | 3 |
| 438 | 591 |  | 4 | 0.3 | <1 |
| 439 | 592 |  | 5 | 0.4 | <1 |

Assay Example 2

Antineoplastic Effects of Histone Deacetylase Inhibitors on Human Tumor Xenografts *In Vivo*

[0413] Eight to ten week old female BALB/c nude mice (Taconic Labs, Great Barrington, NY) were injected subcutaneously in the flank area with 2×10^6 preconditioned HCT116 human colorectal carcinoma cells. Preconditioning of these cells was done by a minimum of three consecutive tumor transplantations in the same strain of nude mice. Subsequently, tumor fragments of approximately 30 mgs were excised and implanted subcutaneously in mice, in the left flank area, under Forene anesthesia (Abbott Labs, Geneva, Switzerland). When the tumors reached a mean volume of 100 mm³, the mice were treated intravenously, subcutaneously, or intraperitoneally by daily injection, with a solution of the histone deacetylase inhibitor in an appropriate vehicle, such as PBS, DMSO/water, or Tween 80/water, at a starting dose of 10 mg/kg. The optimal dose of the HDAC inhibitor was established by dose response experiments according to standard protocols. Tumor volume was calculated every second day post infusion according to standard methods (e.g., Meyer et al., *Int. J. Cancer* 43: 851-856 (1989)). Treatment with the HDAC inhibitors according to the invention caused a significant reduction in tumor weight and volume

relative to controls treated with vehicle only (*i.e.*, no HDAC inhibitor). In addition, the level of histone acetylation when measured was significantly elevated relative to controls. Data for selected compounds are presented in Table 6. FIG. 1 shows the full experimental results for compound 106, which inhibits tumor growth by 80%. Figs. 2-10 show the results of additional compounds tested.

Table 6

Antitumor Activity in HCT 116 Colorectal Tumor Model *In Vivo*

| Compound | % Inhibition of Tumor Growth |
|----------|------------------------------|
| 106 | 80 ^a |
| 126 | 62 ^b |
| 9 | 51 ^b |
| 87 | 30 ^b |
| 157 | 66 ^a |
| 167 | 58 ^a |
| 15 | 26 ^b |
| 168 | 26 ^b |
| 16 | 50 ^b |
| 154 | 23 ^a |
| 98 | 52 ^a |

a: 20 mg/kg *i.p.*

b: 40 mg/kg *i.p.*

Table 7

Antineoplastic Effects Of Histone Deacetylase Inhibitors On Nude Mice Xenograft Models

| cpd | % Inhibition Of Tumor Growth | | | | |
|----------|------------------------------|----------------------|--------------------------|----------------------------|--------------------------|
| | A 549 (<i>p.o.</i>) | SW48 (<i>p.o.</i>) | A 549 (<i>i.p.</i>) | HCT 116 (<i>i.p.</i>) | SW 48 (<i>i.p.</i>) |
| 106 | 40% (70 mg/kg) | 16% (60 mg/kg) | - | - | - |
| 164 | 42% (70 mg/kg) | 62% (60 mg/kg) | - | 37% (20 mg/kg) | 99% (25 mg/kg) |
| 228 | 45% (70 mg/kg) | 25% (60 mg/kg) | 64% (20 mg/kg) | 45% (20 mg/kg) | 68% (20 mg/kg) |
| 424 b | 67% (50 mg/kg) | 78% (30 mg/kg) | 60% (50 mg/kg) | 77% (75 mg/kg) | 68% (25 mg/kg) |

Assay Example 3

Combined Antineoplastic Effect of Histone Deacetylase Inhibitors and Histone Deacetylase Antisense Oligonucleotides on Tumor Cells *In Vivo*

[0414] The purpose of this example is to illustrate the ability of the combined use of a histone deacetylase inhibitor of the invention and a histone deacetylase antisense oligonucleotide to enhance inhibition of tumor growth in a mammal. Preferably, the antisense oligonucleotide and the HDAC inhibitor inhibit the expression and activity of the same histone deacetylase.

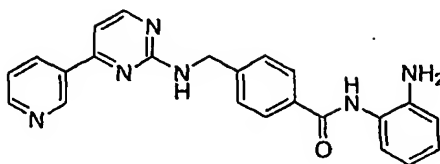
[0415] As described in Example 126, mice bearing implanted HCT116 tumors (mean volume 100 mm³) are treated daily with saline preparations containing from about 0.1 mg to about 30 mg per kg body weight of histone deacetylase antisense oligonucleotide. A second group of mice is treated daily with pharmaceutically acceptable preparations containing from about 0.01 mg to about 5 mg per kg body weight of HDAC inhibitor.

[0416] Some mice receive both the antisense oligonucleotide and the HDAC inhibitor. Of these mice, one group may receive the antisense oligonucleotide and the HDAC inhibitor simultaneously intravenously via the tail vein. Another group may receive the antisense oligonucleotide via the tail vein, and the HDAC inhibitor subcutaneously. Yet another group may receive both the antisense oligonucleotide and the HDAC inhibitor subcutaneously. Control groups of mice are similarly established which receive no treatment (e.g., saline only), a mismatch antisense oligonucleotide only, a control compound that does not inhibit histone deacetylase activity, and a mismatch antisense oligonucleotide with a control compound.

[0417] Tumor volume is measured with calipers. Treatment with the antisense oligonucleotide plus the histone deacetylase protein inhibitor according to the invention causes a significant reduction in tumor weight and volume relative to controls.

We claim:

1. A histone deacetylase inhibitor of formula (1):



or pharmaceutically acceptable salt.

2. A composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.
3. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a compound according to claim 1.
4. A method of inhibiting histone deacetylase in a cell, the method comprising contacting a cell with a composition according to claim 2.

Antitumor Activity of MethylGene Small Molecule HDAC Inhibitors in HCT116 Human
Colorectal Tumor Model

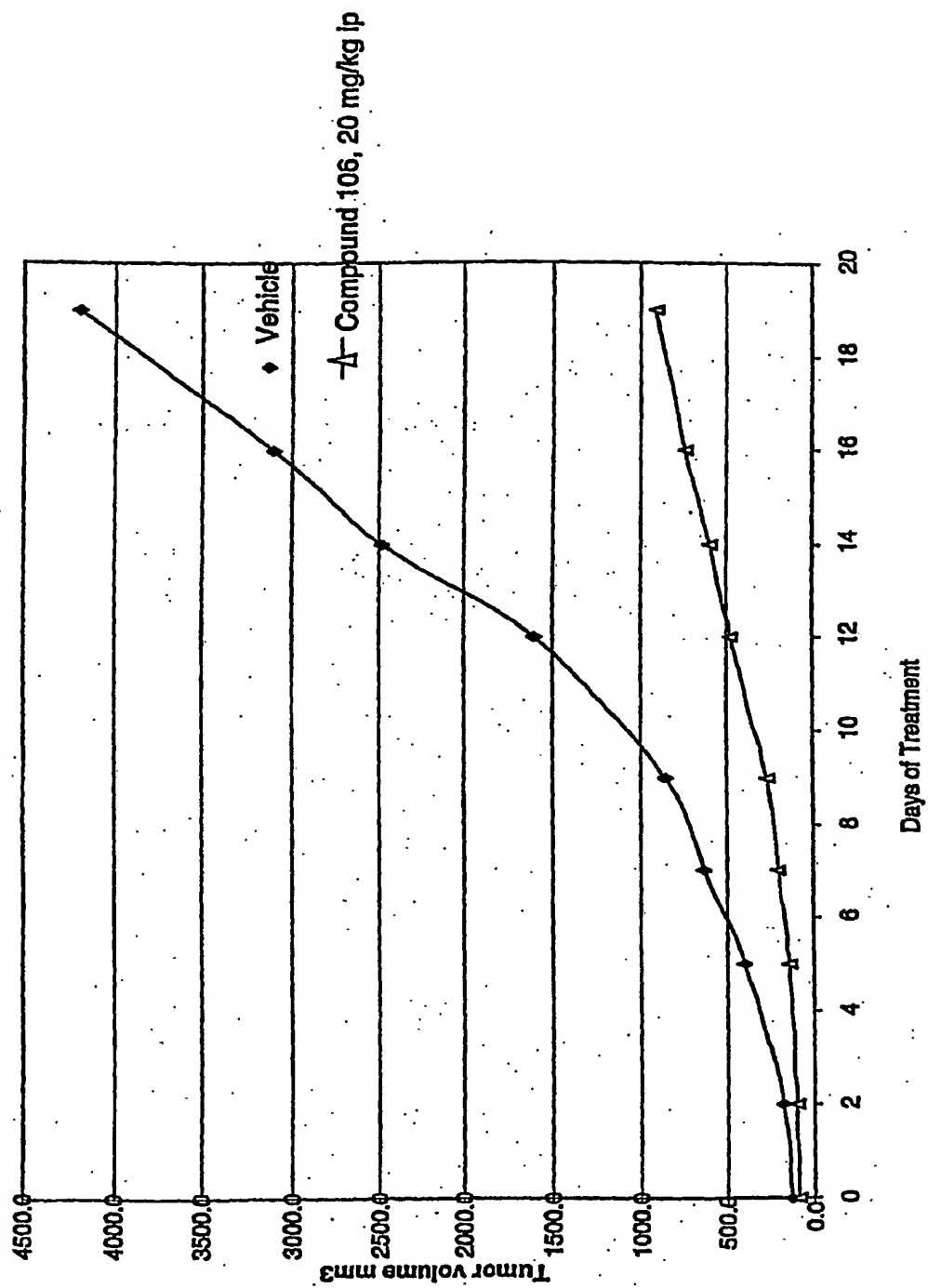


FIG. 1

**Inhibition of A549 Human Lung Cancer Tumor Growth by
Compound 106 After Intraperitoneal Administration**

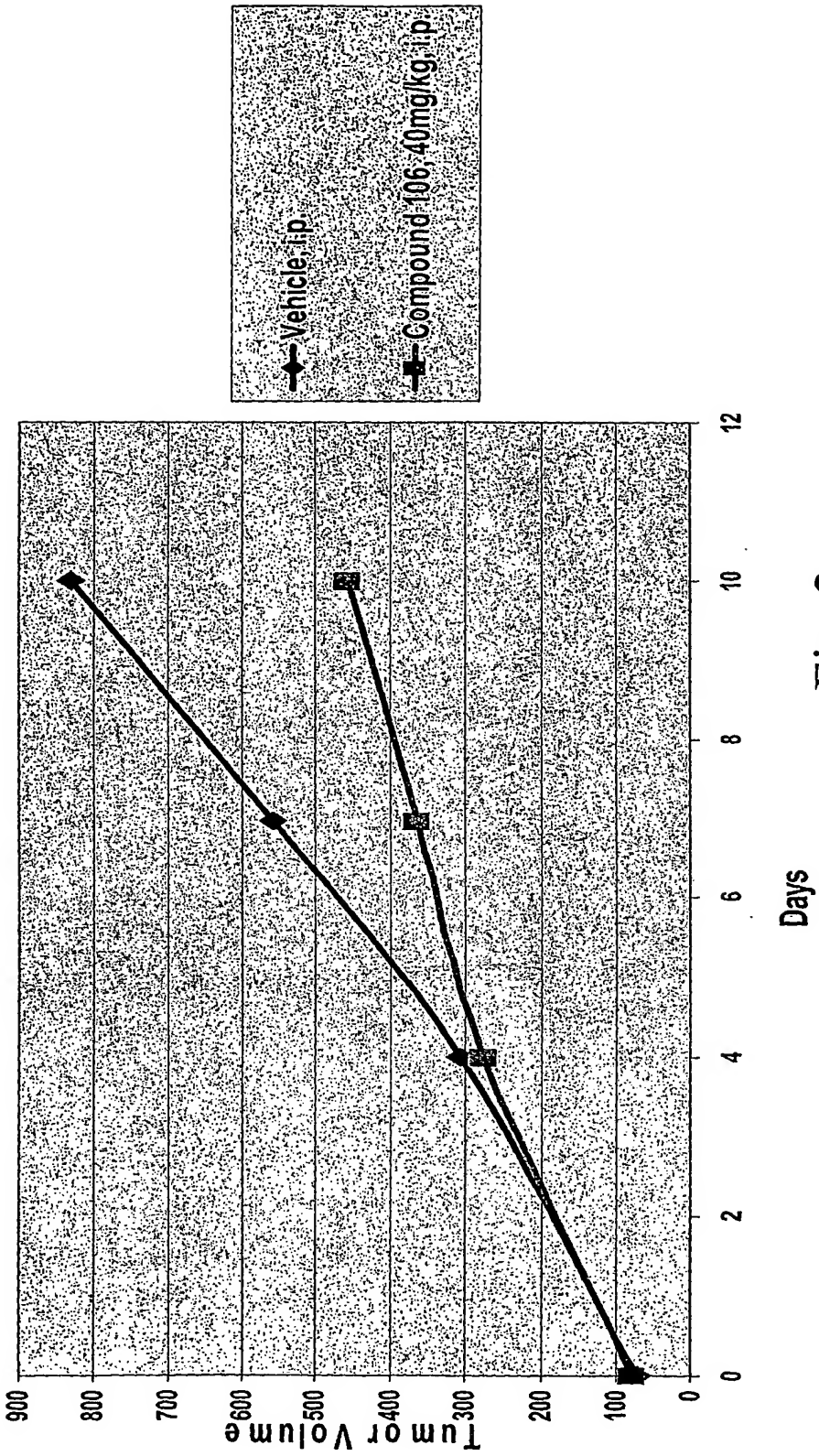
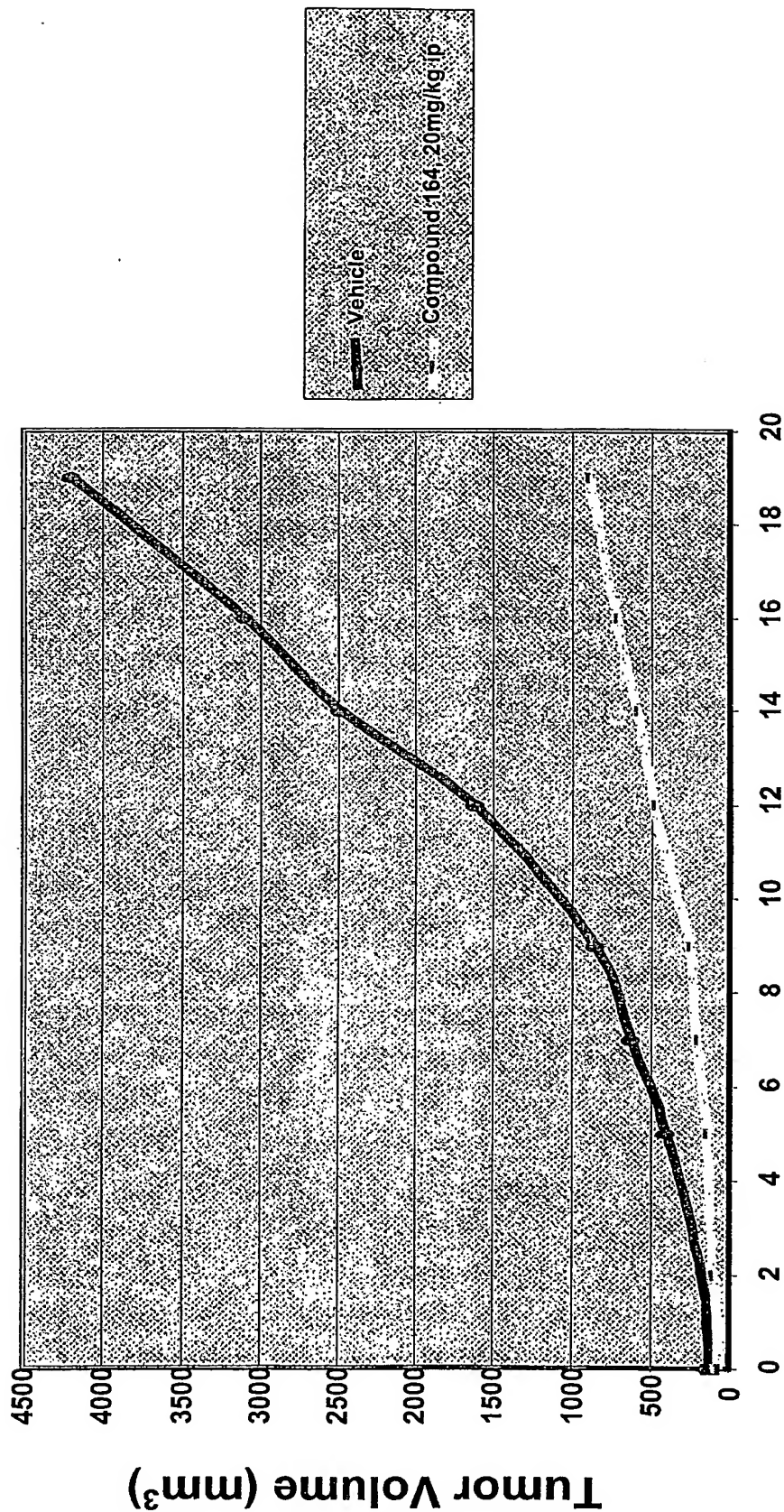


Fig. 2

Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 164 after Intraperitoneal Administration



Days of Treatment

Fig. 3

Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 228 After Oral Administration

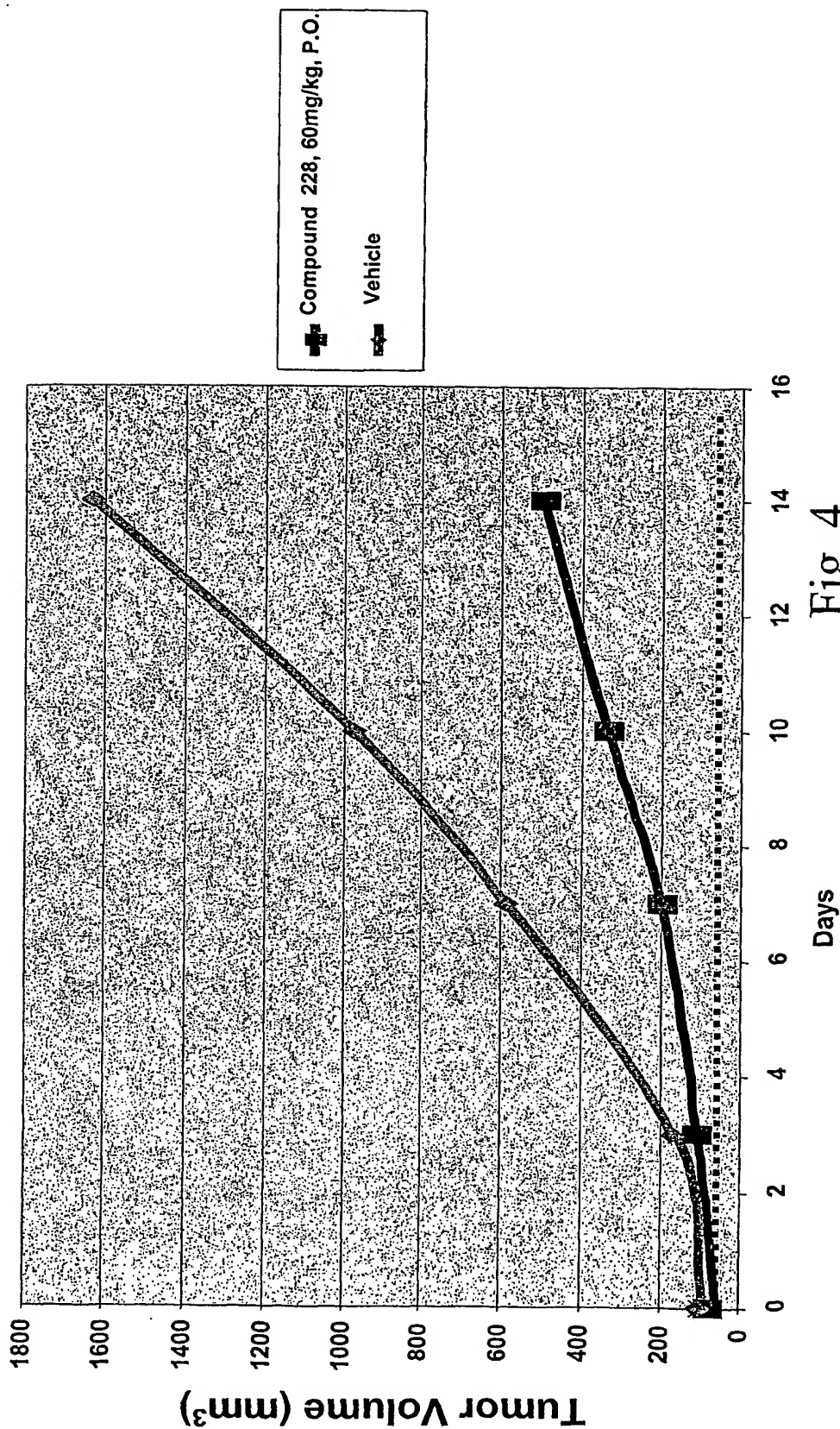


Fig. 4

Inhibition of HCT116 Human Colorectal Tumor Growth by Compound 311 after Intraperitoneal Administration

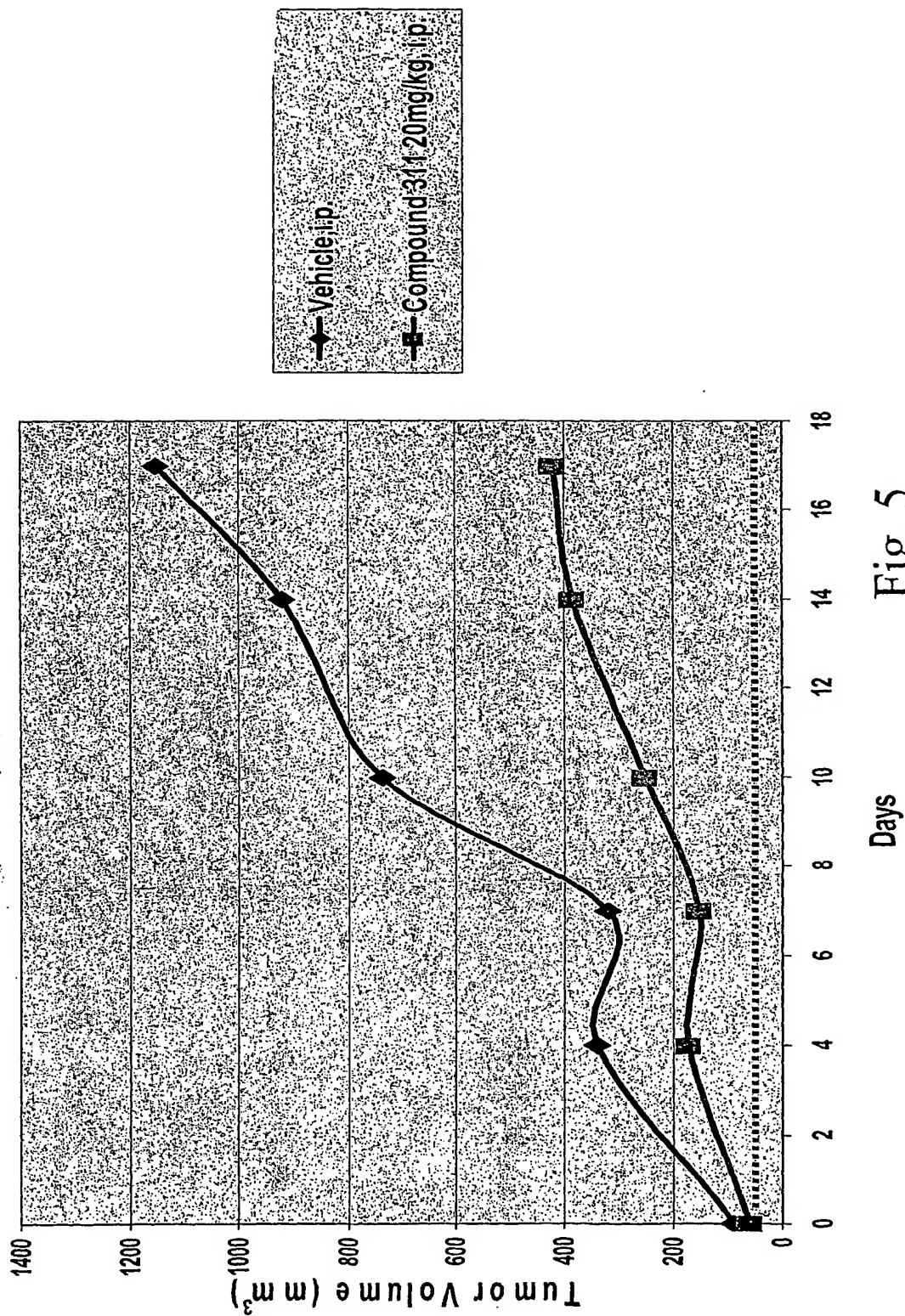


Fig. 5

Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth
by Compound 376 After Oral Administration

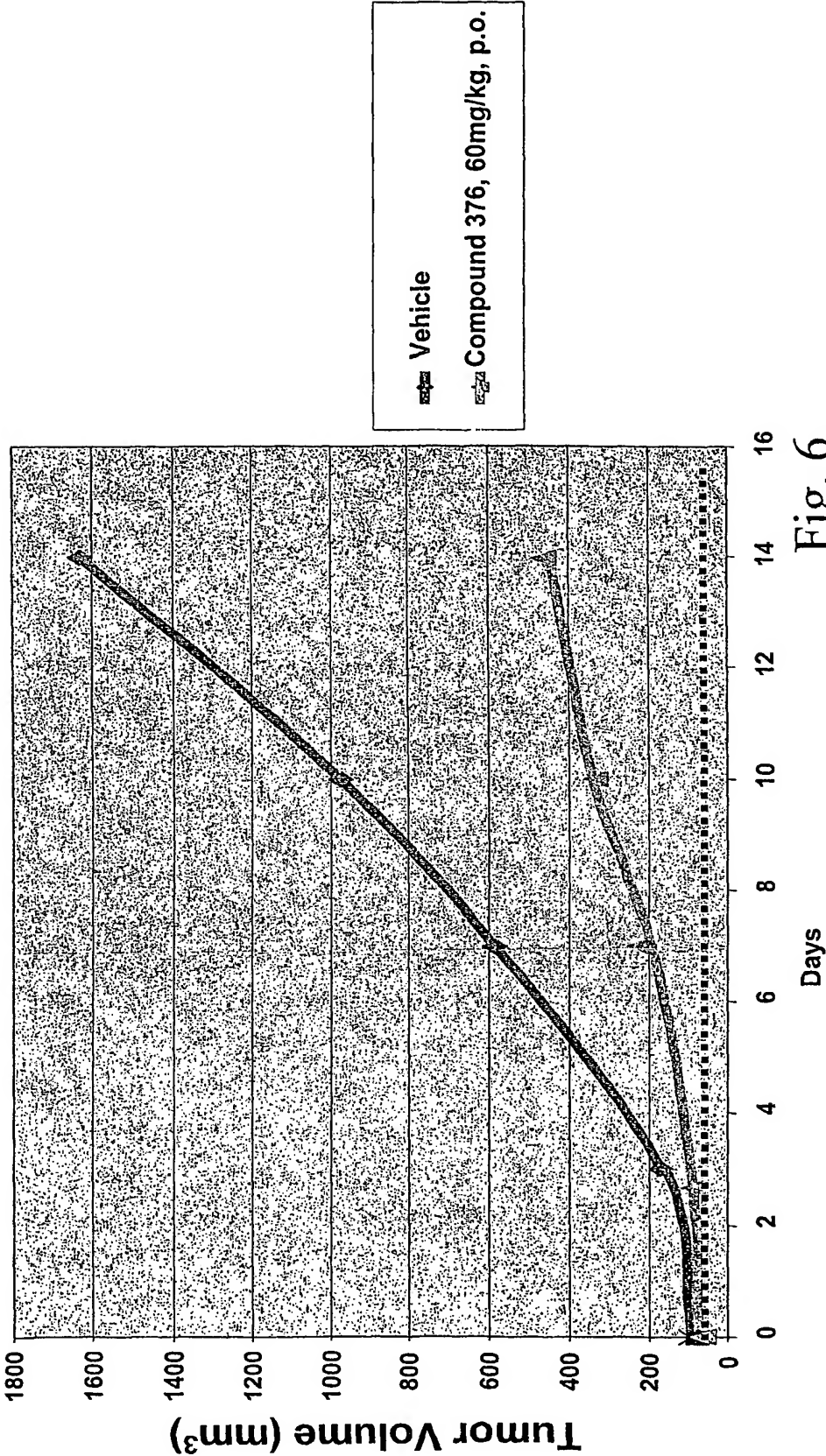


Fig. 6

Inhibition of A549 Human Lung Cancer Tumor Growth by
Compound 402 After Intraperitoneal Administration

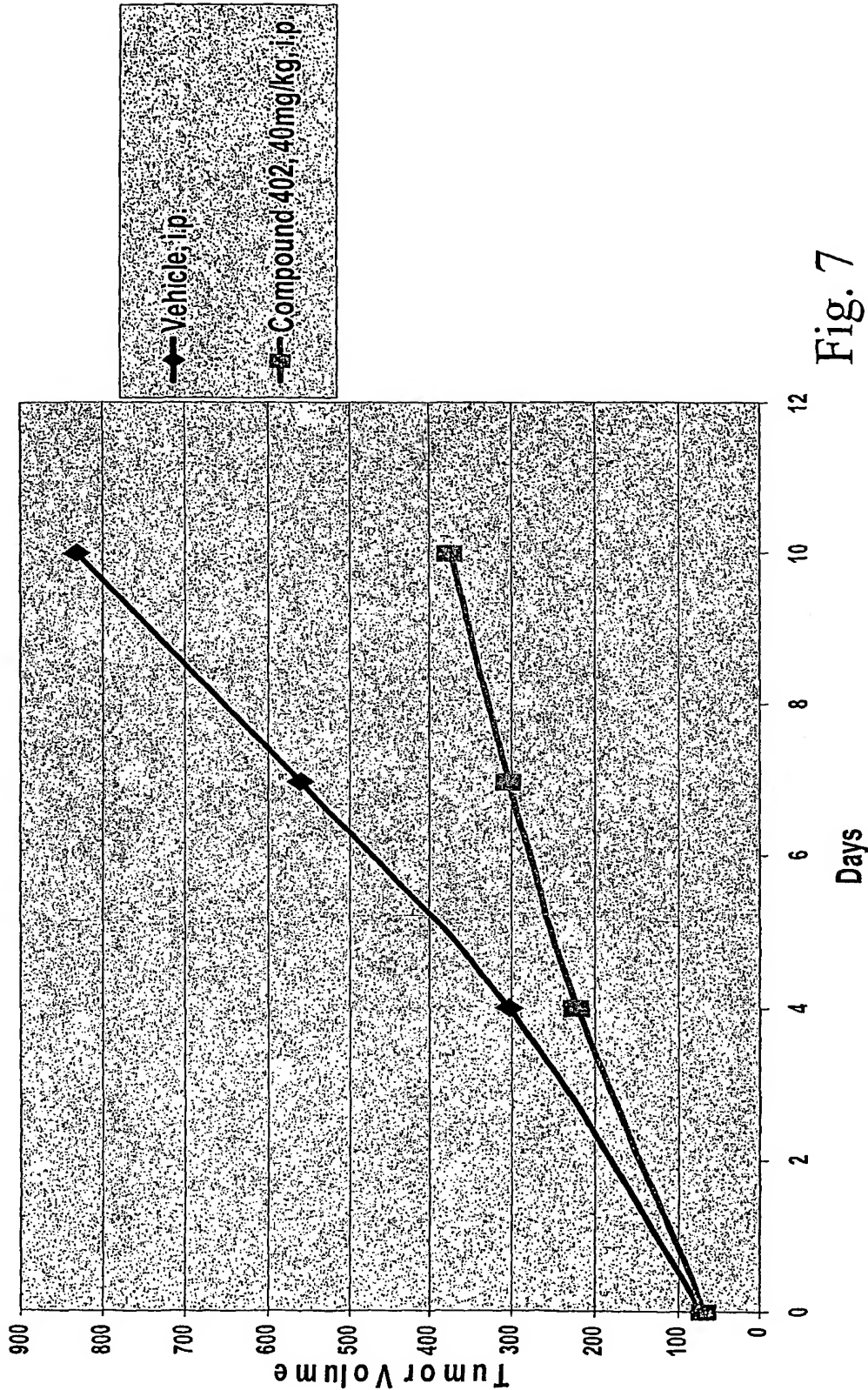


Fig. 7

Inhibition of Panc-1 Human Pancreatic Cancer Tumor Growth by Compound 421 After Oral Administration:

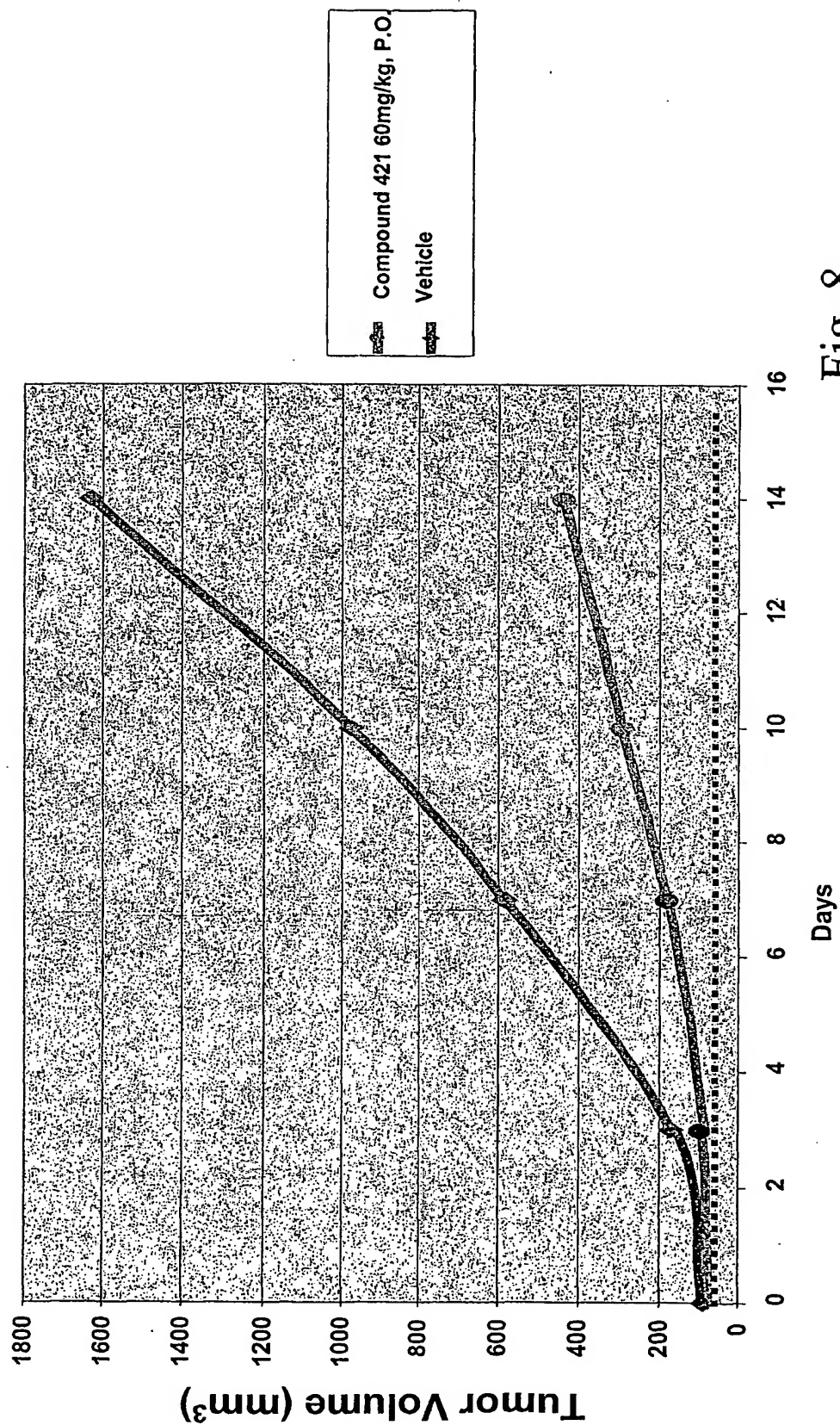


Fig. 8

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Intraperitoneal Administration

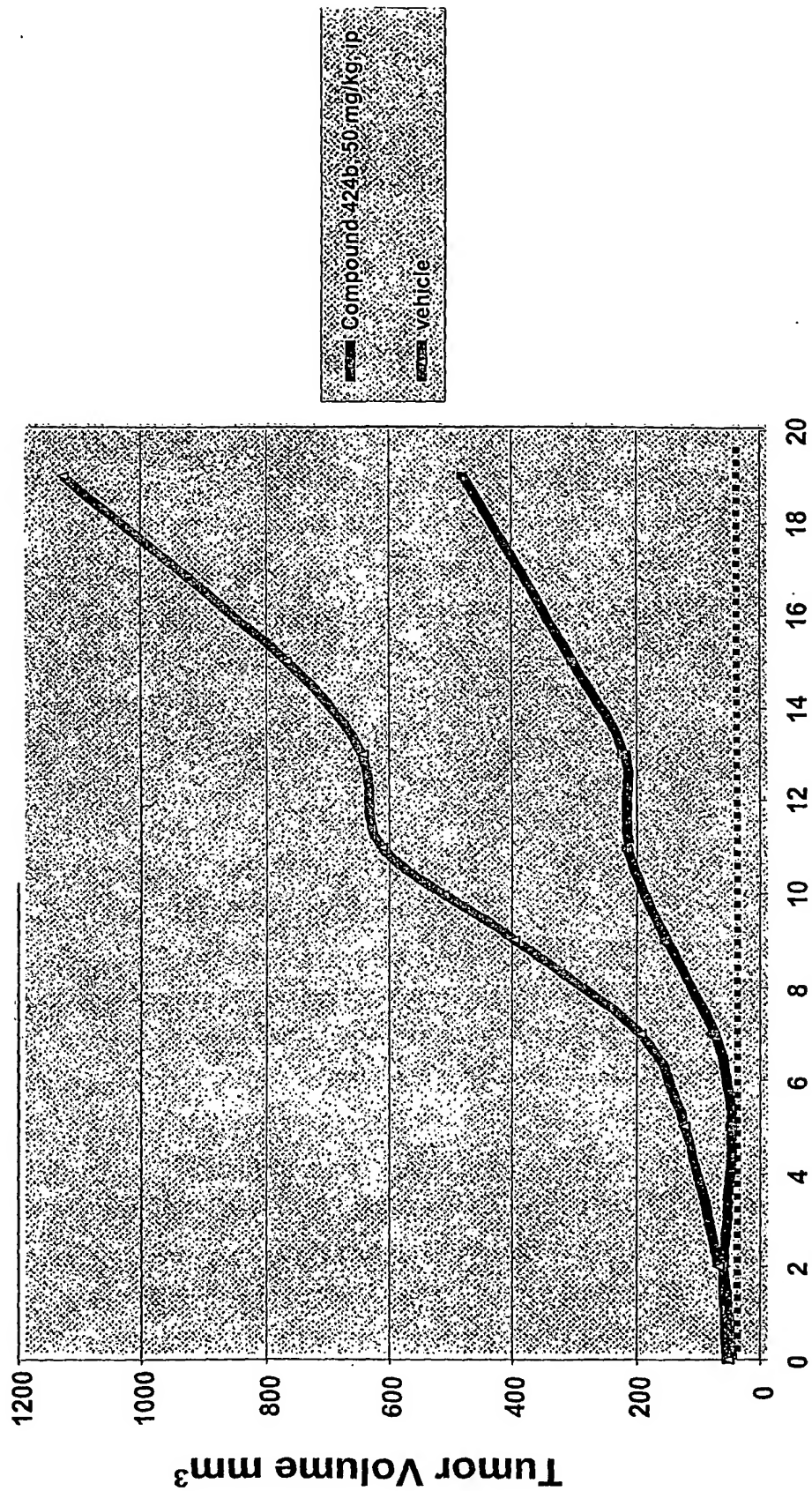
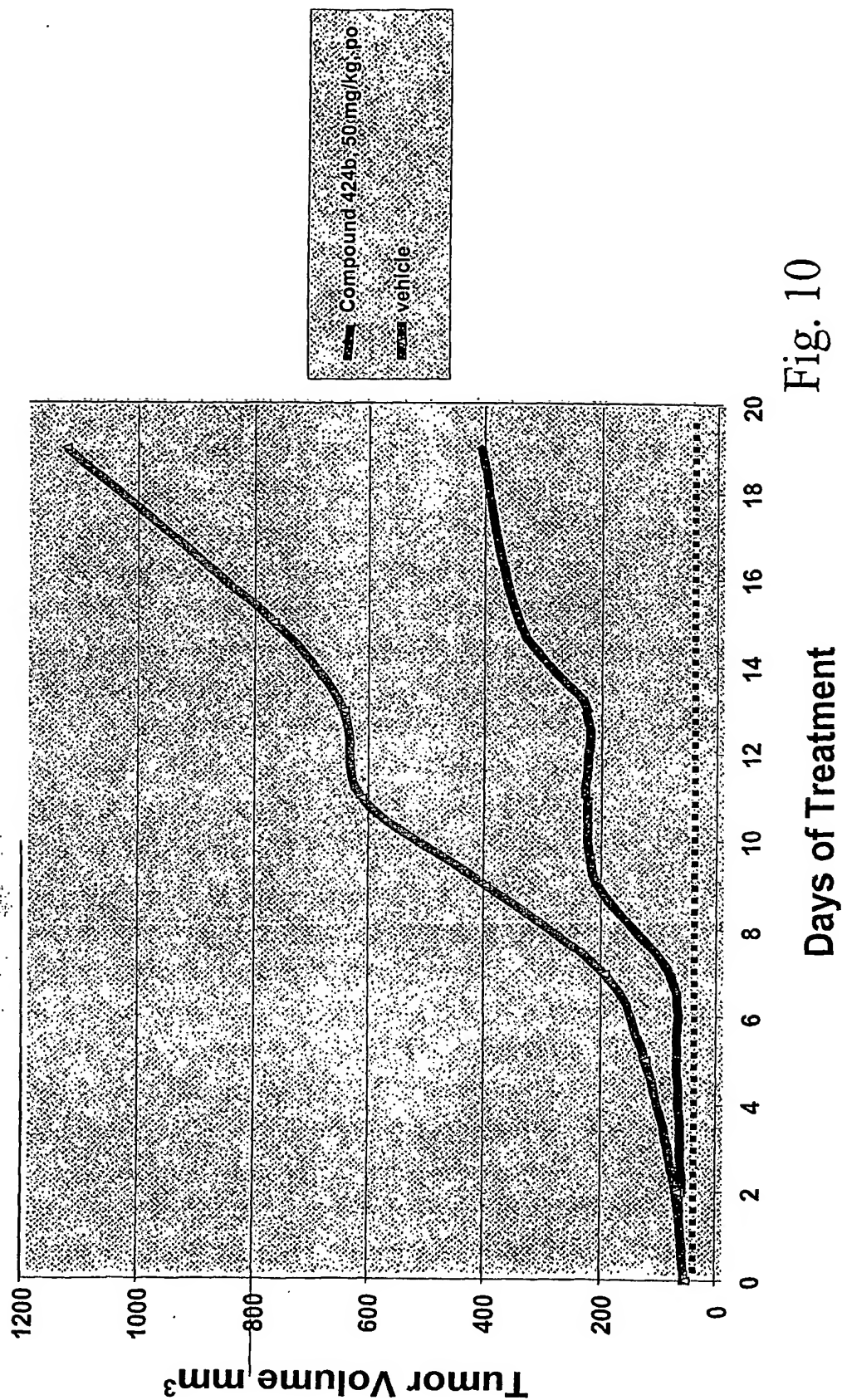


Fig. 9

Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 424b after Oral Administration



Inhibition of A549 Human Lung Cancer Tumor Growth by Compound 570 after Intraperitoneal Administration

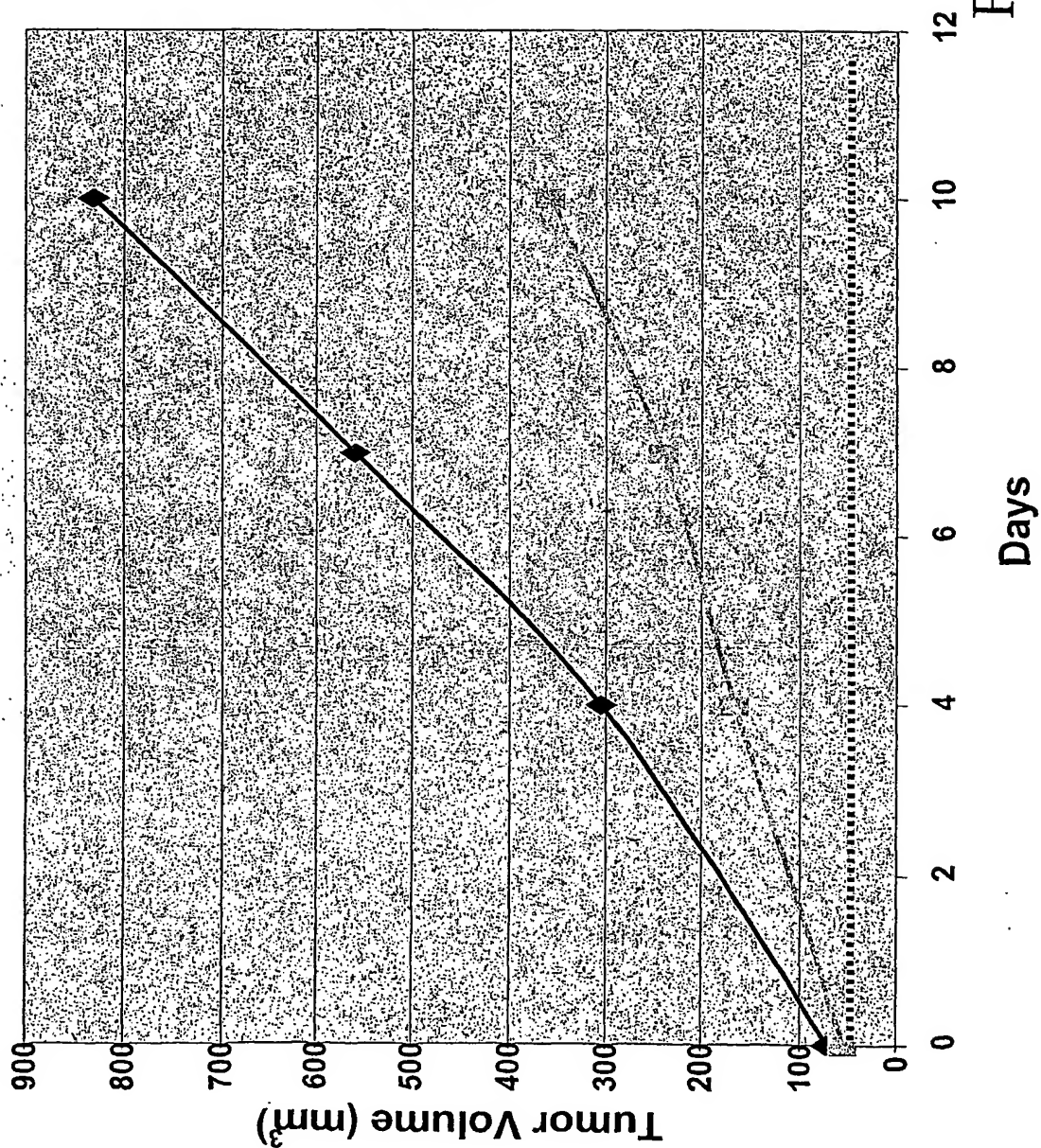


Fig. 11

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA2004/000139

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 A61K31/506 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
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| Y | EP 0 847 992 A (MITSUI CHEMICALS INC) 17 June 1998 (1998-06-17) claim 1; examples | 1-4 |
| P,X | WO 03/024448 A (MORADEL OSCAR ; DELORME DANIEL (CA); LEIT SILVANA (CA); METHYLGENE INC) 27 March 2003 (2003-03-27) page 179; example 433 | 1-4 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

9 July 2004

Date of mailing of the international search report

19/07/2004

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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